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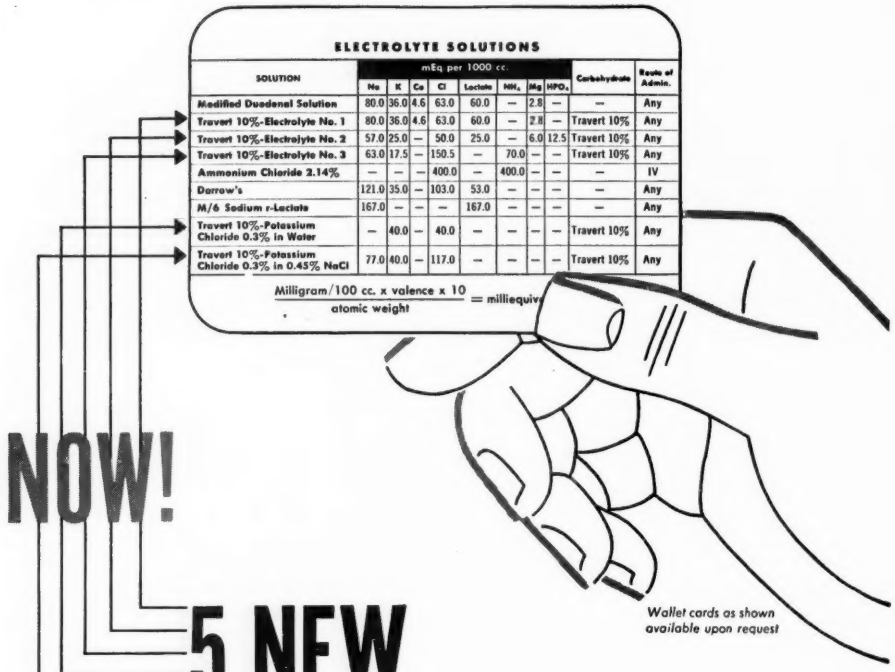
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Travert 10%-Electrolyte No. 3 63.0 17.5 — 150.5 — 70.0 — — Travert 10% Any
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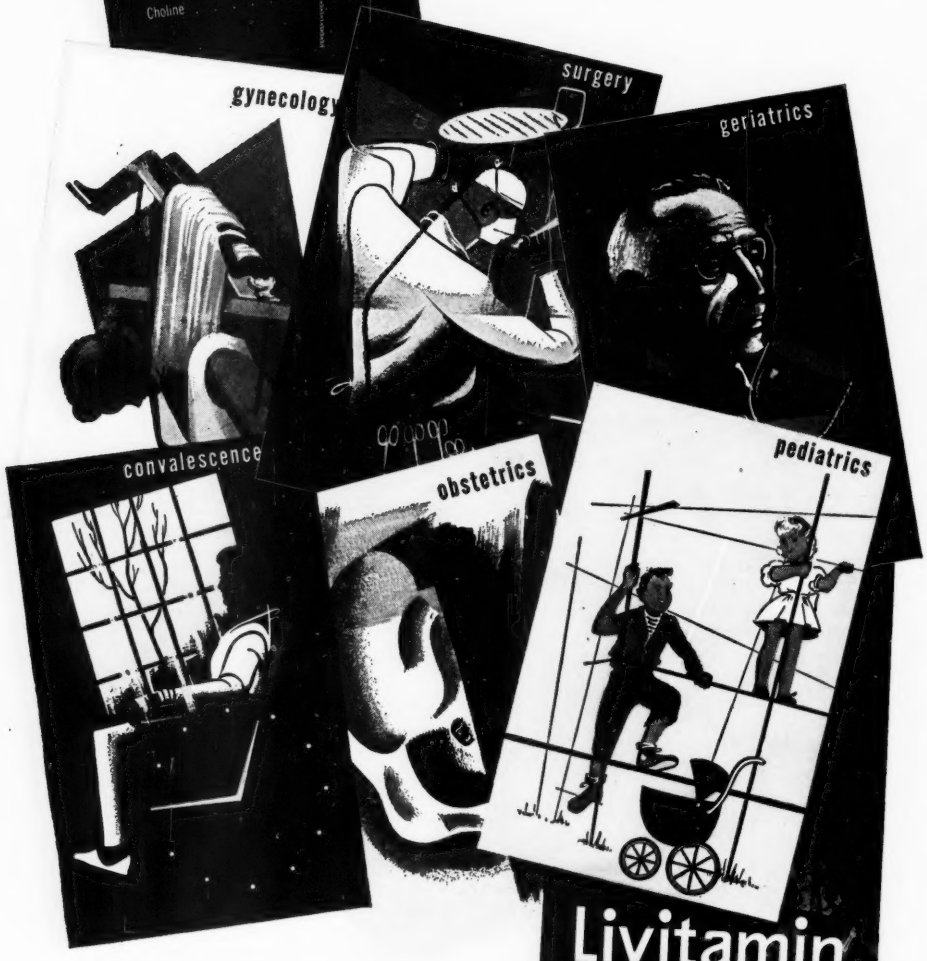

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SURGERY
GYNECOLOGY AND OBSTETRICS

VOLUME 97 JULY, 1953 NUMBER 1

DEFORMITIES OF THE URINARY TRACT WITH CONGENITAL ABSENCE OF THE VAGINA

JOHN T. PHELAN, M.D., VIRGIL S. COUNSELLER, M.D., F.A.C.S., and LAURENCE F. GREENE, M.D., Rochester, Minnesota

THE incidence of congenital absence of the vagina varies from 1 to 5,000 as reported by Engstad, to about 1 to 100,000 female patients as claimed by Owens, from Charity Hospital, New Orleans, Louisiana. Increasing numbers of cases of this infrequent anomaly are being reported.

One of us (Counseller) has emphasized the importance of complete study of the urinary tract before surgical correction of the vaginal malformation is undertaken. To secure further information concerning the urinary tracts of patients with vaginal agenesia, we have examined the records of 129 patients with this anomaly who were seen at the Mayo Clinic. Before the results of this examination are reported, however, a few paragraphs will be devoted to fundamentals.

EMBRYOLOGY

Detailed discussion of the embryology of the urinary and genital tracts is not pertinent to this presentation. It is sufficient to recall that both systems arise from the intermediate cell mass. In view of this common embryologic origin, the simultaneous occurrence of anomalies of the genital and urinary tracts is to be expected.

From the Department of Surgery, Mayo Foundation, and the Division of Surgery and Section of Urology, Mayo Clinic, Rochester, Minnesota.

Brief discussion of the embryologic development of the vagina, however, is in order. According to Wharton, the first stage in formation of the vagina is fusion of the lower portions of the müllerian ducts. The epithelium of the urogenital sinus becomes stratified and fuses with the stratified epithelium of the fused müllerian ducts. Proliferation of the stratified epithelium converts the lumen of the vagina into a solid cord. Thus, proliferation begins at the points of union between müllerian ducts and urogenital sinus. In this manner the entire vaginal canal, up to the future cervix, becomes a solid core of thick, stratified epithelium. The vaginal cavity is formed by degeneration of the cells in the center of this solid vaginal cord. It must be mentioned, however, that some authors believe that the vagina develops solely from the müllerian ducts, while others believe it arises entirely from the urogenital sinus.

EXPERIMENTAL DATA

A small body of experimental data concerning anomalies of the urinary and genital tract is being collected and the close relationship between these two systems is apparent. Boyden was able to traumatize the wolffian duct of chick embryos and thus prevent development of a kidney on the same side. O'Connor, working with Amphibia, injured the prone-

phric duct and noted failure of development of the mesonephros. Gruenwald demonstrated that development of the müllerian duct was dependent on normal development of the wolffian duct. Burns, working with opossums, was able to produce histologic changes in the urogenital sinus of these animals by giving them estrogenic material. Greene, Burrill, and Ivy produced partial atresia of the distal third of the vagina in mice born of mothers who had received large doses of estrogen.

ANALYSIS OF DATA

The 129 cases of vaginal agenesia which form the basis of this study are divided into two groups: (1) those in which excretory urography and, in some instances, cystoscopy were performed (72 cases) and (2) those in which urologic investigation was not performed (57 cases). Anomalies of the urinary tracts of some patients of the latter group were observed at the time of general physical examination or surgical exploration as will appear.

RESULTS OF UROLOGIC INVESTIGATION

Significant anomalies. Urographic evidence of abnormalities of the upper part of the urinary tract were observed in 26 of the 72 patients whose urinary tracts were studied. The significant anomalies which were observed in 18 of the 26 patients are as follows: renal agenesia of the right kidney in 4 patients and of the left in 6; renal ectopia of the right kidney in 3 patients, of the left in 2, and of both in 1; unilateral fused kidney on the right in 1 patient; ureteropelvic obstruction of both kidneys in 1 patient.

Cystoscopic examinations were performed on 14 of the 18 patients whose anomalies were significant. In 3 cases in which urography had revealed renal agenesia, absence of the corresponding ureteral orifice and ridge was noted. Three of the patients who underwent cystoscopic examination had complained of symptoms referable to the lower part of the urinary tract. The mucosa at the vesical neck of 1 of these 3 patients was hyperplastic. The remaining 2 patients complained of partial urinary incontinence and, on cystoscopic examination, definite defects were found in the floor of the urethra. Both of these patients reported that they had undergone unsuccessful attempts at surgical construction of a vagina.

Minor congenital anomalies. Mild obstruction at the ureteropelvic junction and malrotation of the kidneys were observed in the remaining 8 of the 26 cases.

URINARY ANOMALIES DETECTED AT GENERAL PHYSICAL EXAMINATION OR SURGICAL EXPLORATION

In the past, surgical procedures for correction of vaginal agenesia required abdominal exploration. At the time of these operations certain anomalies of the urinary tract were noted. In addition, anomalies of the urinary tract were observed on physical examination. The anomalies noted by these means consisted of ectopia of the kidneys in 3 instances and dilatation of the urethra in 4 cases. The etiology of the dilatation of the urethra was not apparent.

COMMENT AND SUMMARY

One of us (Counseller) has recorded an increased occurrence or an increased incidence of diagnosis of pelvic abnormalities, such as endometriosis, hydrocolpos, ovarian cyst, and the like, and has commented on the fact that a hydronephrotic kidney in the pelvis may be indistinguishable on physical examination from such a condition. Removal of such a kidney may be difficult because of its fixed position and abnormal blood supply. From the patient's point of view it is important that she be made acquainted with the fact if she has a solitary, ectopic, fused, or hydronephrotic kidney.

The importance of these anomalies, as well as of others of the urinary tract, is evident if surgical formation of a vagina is contemplated. The presence of an ectopic pelvic kidney may interfere with securing proper depth of the new vagina. A pelvic kidney and its ureter may be traumatized during the surgical procedure and such trauma is particularly significant if the pelvic kidney represents a solitary kidney.

Urographic evidence of anomalies of the urinary tract was observed in 26 of 72 pa-

tients with vaginal agenesia who had undergone examination. Of these anomalies 18 were significant and, of the 18, those of most frequent occurrence were renal agenesia and renal ectopia. Physical examination and surgical exploration revealed 7 additional cases of anomaly of the urinary tract. It is apparent, therefore, that all patients with vaginal agenesia should undergo urologic examination, inasmuch as a fourth of our patients had significant anomalies of the urinary tract.

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THE SURVEY ROENTGENOGRAMS AS AN AID IN THE DIAGNOSIS OF ACUTE ABDOMINAL CONDITIONS

W. WAYNE SANDS, M.D., Santa Monica, California

THE diagnosis of acute abdominal conditions is an exacting and perplexing task for all physicians. If a physician is armed only with his clinical training and reasoning, it may be an arduous and perilous adventure. For the physician who has colleagues and laboratory aids at his command to guide and prompt his clinical judgment, the riddle of the acute abdominal disorder is more easily solved. However, the effectiveness of his diagnostic aids may be greatly blunted unless the full scope of their usefulness and limitations is well understood. In such abdominal emergencies an early diagnosis is important. Hesitancy may be fatal, or operative procedures may be needless or delayed until a more favorable time. A specific diagnosis aids the surgeon. For example, a costovertebral incision may be desired for a perinephritic abscess or an anterior abdominal incision for an appendiceal abscess. Survey films are valuable aids in the diagnosis of acute abdominal conditions. Therefore, it is the purpose of this paper to outline the roentgenographic essentials necessary for proper interpretation and the means by which these roentgenograms may be made more useful. Some of the abdominal diseases in which they are of assistance will also be considered.

The term "survey films" when applied to the abdomen has many synonyms, some of which are: "plain films," "flat films," "KUB," "preliminary films," and "scout films." In this discussion the plural survey films will be used. The term will mean a series of abdominal roentgenograms taken without the previous introduction of contrast media (such as barium or air) or preparation of the patient by enemas or cathartics. It is also assumed that the consultant in radiology is well acquainted with the patient's clinical history and physical examination before attempting to interpret the survey films.

From the Department of Radiotherapy, Cedars of Lebanon Hospital, Los Angeles.

Schwarz, in 1914, made the first efforts at roentgen examination in cases of acute intestinal obstruction. Since that time, many radiologists have emphasized the usefulness of survey films as diagnostic aids in acute abdominal catastrophes. There has been some reluctance in ordering survey films of the abdomen although roentgenographic examinations are casually ordered for the chest which can seldom match the urgencies or dangers of the abdomen. Rigler (6) has suggested that this reluctance is due to the radiologist who avoids night work or the tendency to assign night hours to the younger and less well trained technicians. These are well aimed criticisms, for it is obvious that a roentgen examination of the abdomen must have competent interpretation and technically good films if it is to benefit the clinician.

TECHNIQUE

One reason for poor films is the bedside examination. Although sometimes necessary, much of the finer detail is lost in this procedure. Examination of the abdomen is best done with a Bucky-Potter diaphragm which is not available on a portable unit. A complete roentgen examination for an acute abdominal condition should include at least 4 films: a high and low supine film, an upright film, and a posteroanterior chest film. A technique giving a wide latitude of contrast is preferable. Wangensteen has suggested placing a metallic marker, such as a coin, on the umbilicus during the prone examination. Distended bowel is magnified on the roentgenogram, and this marker estimates comparatively the degree of distortion. In a critically ill patient the upright examination may be substituted with a left lateral decubitus position and a horizontal beam. This, like the upright film, will detect free

air and fluid levels. A posteroanterior chest film is a necessary part of a complete examination of the abdomen. It is well known that thoracic diseases may cause abdominal pain. This is due to pain referred from the thorax to the abdominal wall and viscera by way of the intercostal, phrenic, or sympathetic nerves. Pneumonia and acute pneumothorax may commonly simulate abdominal emergencies. Other thoracic diseases mimicking acute abdominal conditions are dissecting aortic aneurysm, ruptured esophagus, acute pericarditis, Pott's abscess, osteoarthritis, and vertebral fractures. In all of these a chest film may explain the abdominal symptoms.

THE ANATOMY AND THE DENSITIES OF THE SURVEY FILM

Before interpreting the roentgenologic appearance of abdominal diseases, it is well to review the landmarks of the normal anteroposterior film (Fig. 1). It is also necessary to have an appreciation of the manner in which materials of varying density are contrasted on the roentgenogram (Fig. 2). The more dense a substance, the greater the absorption of roentgen rays and the whiter the film behind the density. On the roentgenogram these differences in density, although sometimes slight, contrast and identify the contents of the abdomen. The following discussion and illustrations will show specifically how these shadows and highlights become clues in the diagnosis of abdominal diseases.

Gas (Fig. 2a). Gases offer little absorption of roentgen rays. If only a gas is interposed between the roentgen-ray tube and the film cassette, there will be considerable darkening of the x-ray film. Gas, contrasting markedly with all other substances, enables the gas-containing organs to be located and identified. Gas is normally seen in the stomach, duodenal bulb, and large bowel of the adult (Fig. 1). The origin of intraluminal gas will be considered later. Its presence outside the gastrointestinal tract is definitely abnormal. Extragastrointestinal gas is either free in the peritoneal cavity or localized within abscesses, soft tissues, or the retroperitoneum. Free gas within the peritoneal cavity may be present following an abdominal operation or

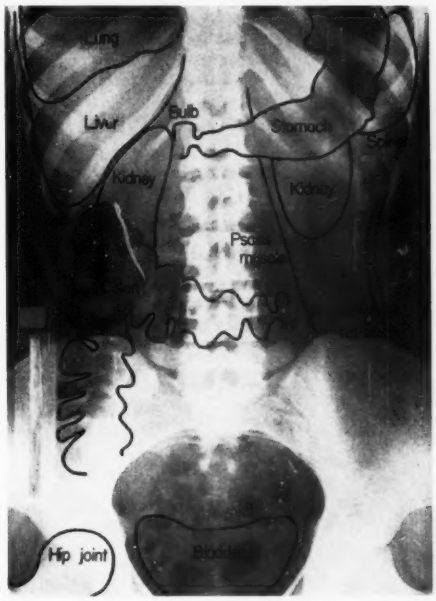

Fig. 1. Normal anteroposterior abdominal roentgenogram.

the rupture of a hollow viscus. The upright or left lateral decubitus positions will detect very small amounts of air beneath the diaphragm or above the right lobe of the liver. Studies on cadavers show that as little as 5 cubic centimeters of air can be visualized roentgenographically beneath the diaphragm in the upright position. Gas localized in the soft tissues is seen following injury, operation, or infection. Gillies reported interstitial emphysema due to the colon bacillus. Gas due to the proteus or colon bacilli or anaerobic streptococci may form bubbles within retroperitoneal or abdominal abscesses. Weens reported 4 cases of retroperitoneal abscesses with gas formation. Bird, Fissel, and Young observed 2 cases of ruptured appendix with clusters of gas vesicles within resulting abscesses. The latter authors recommended stereoscopic views of the abdomen in order to determine whether these gas bubbles were outside the bowel. It is believed that this finding of localized gas vesicles in abdominal and retroperitoneal abscesses is more common than the literature indicates. During the

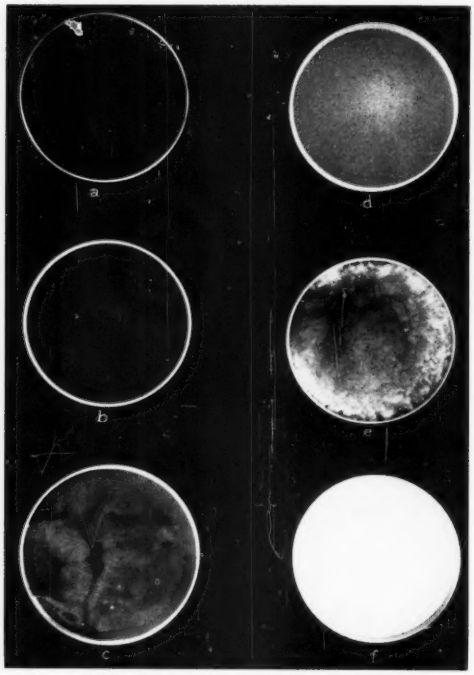

Fig. 2. Illustration demonstrating the appearance of materials of varying density on the abdominal roentgenogram: a, gas, b, fat, c, soft tissues, d, liquid, e, calcium, f, metal.

period 1947 to 1950, we (8) have noted 10 abscesses with roentgenographically demonstrable gas.

Fat (Fig. 2b). On the film, fat is less opaque than normal tissues such as muscle or bowel. Dermoid cysts, sometimes seen in the pelvis, appear as rarefied areas which are well delineated from more opaque tissues such as bowel or bone. The psoas muscles, kidneys, and properitoneal fat lines are well visualized because they are either surrounded by or contain fat (Fig. 1).

Liquid (Fig. 2d). Except for urine in the bladder or fluid in the stomach, a fluid density on the survey films is usually abnormal. Nephritic or appendiceal abscesses may be suspected when fluid densities appear in the kidney or cecal regions. Fluid levels are often seen in abdominal or subphrenic abscesses.

Calcium (Fig. 2e). Calcium is almost as dense as metal and is seen normally in the abdomen, ribs, vertebrae, and calcified lymph nodes. Often, however, calcification within a biliary or urinary tract calculus, the adrenals, or an abdominal aneurysm suggests the nature of abdominal symptoms.

Metal (Fig. 2f). When metallic sutures are seen in the abdominal soft tissues, it may be suspected that an intestinal obstruction is due to adhesions from a previous operative procedure. Knife blades, shell fragments, and other metallic foreign bodies may rather simply explain the cause of an acute abdominal condition.

ILEUS, BOWEL OBSTRUCTION, AND PERITONITIS

With the normal survey film and its contrasting densities well in mind, it becomes more simple to consider specific abdominal diseases. Few things plague the radiologist so persistently as the interpretation of distorted and displaced bowel segments. In the differentiation of bowel obstructions the sins of omission are particularly apt to haunt him.

Jejunum, ileum, and colon when distended with gas have characteristic markings which allow them to be identified roentgenographically (Fig. 3). Figure 3 shows the difference between gas distended segments of jejunum, ileum, and colon. The segments of colon show the haustral folds and are often difficult to differentiate from jejunum. However, the haustral folds, unlike the jejunal valvulae conniventes, usually do not traverse the complete width of the bowel (Fig. 3a). The distal ileum lacks specific markings and is described by Wangensteen as being "characterless" (Fig. 3b). The jejunal markings resemble herring bones and are usually not obliterated even if the bowel is tremendously dilated (Fig. 3c). In the illustration, portions of the bowel wall have retracted from the paraffin block and are clearly seen. On the survey films we usually see only the gas column within the lumen and not the bowel wall. When either side of the bowel is surrounded by gas, the wall is clearly seen which is good evidence of free air within the abdominal cavity.

Ileus (Fig 4). Ileus may be seen following operation, cystoscopy, intravenous urography, apprehension, or conscious air sucking. The

survey film shows gas throughout *both the small and large bowel.* The large bowel with its distinguishing haustral markings is seen in the normal anatomic position about the periphery of the abdomen. The moderately distended small bowel is seen in the center of the abdomen in a mosaic arrangement. There are no hairpin or prominently marked loops of small bowel as seen in obstruction. The distribution of gas within the stomach and small and large bowel, with no gross distention of the bowel lumen, is typical of ileus. The intestinal gas seen in ileus is probably due to the unconscious respiration of air into the gastrointestinal tract following fear or anxiety. The origin of intestinal gas in health and disease will be discussed later.

Intestinal obstruction (Fig. 3c). In obstruction, as in ileus, gas is seen in the small bowel. Unlike ileus, however, the bowel lumen is greatly distended and the markings are prominent. The mosaic appearance of the small bowel in ileus is replaced by coiled, spring-like, and dynamic appearing loops arranged transversely in a stepladder fashion across the abdomen. Figure 3c shows the roentgenographic appearance of an obstructed and gas distended bowel. In a low ileal obstruction both ileum and jejunum might be seen. Thus, the gas patterns of bowel aid us in identifying the bowel loops and locating the site of the obstruction.

The diagnosis of a large bowel obstruction is usually made by identifying a greatly distended colon arranged about the periphery of the abdomen. Usually gas is not seen in the small bowel; however, the ileocecal sphincter is patent in an appreciable number of instances, and this does not always hold true. An early diagnosis of an obstructed sigmoid colon is imperative because of the danger of a ruptured cecum. The ileocecal sphincter, surrounded by circular and oblique muscles, prevents the regurgitation of gas into the small bowel. The combination of the ileocecal check valve and the distal lesion forms a closed loop obstruction. The cecum, greater in diameter than the remainder of the bowel, bears the most pressure and may burst.

Peritonitis. Peritonitis is often a later stage of intestinal obstruction. Following a closed loop or long standing obstruction the bowel walls become congested and show areas of necrosis. A portal is opened for bacteria and intestinal contents into the peritoneal cavity. Following peritoneal soiling, a fibrinopurulent exudate is formed in copious amounts. This exudate accounts for the opacity of the abdominal survey films in peritonitis. The psoas muscles are obscured by overlying fluid and fibrin. The properitoneal fat lines are obliterated by edema and inflammation. If the upright position is employed, fluid levels may be noted in the distended bowel loops.

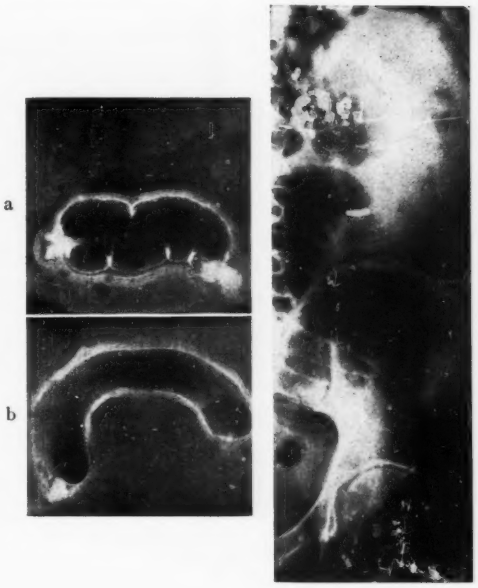

Fig. 3. The normal ileum and colon are taken from a cadaver, filled with air, and set into paraffin blocks. The jejunum is from the film of a patient who at postmortem examination showed a partial jejunal obstruction. This demonstrates the characteristic appearance of obstructed bowel segments.

ORIGIN OF INTESTINAL GAS

The origin of intestinal gas in obstruction and ileus is of interest. Hibbard and Wangensteen (3) determined that intestinal gas in health and obstruction is of atmospheric origin. The classical experiments of Wangensteen and Rea (9) conclusively indicted

Fig. 4. Illustration demonstrates the typical pattern of ileus. Large bowel loops only moderately distended are noted in their normal anatomic position about the periphery of the abdomen. Small bowel loops are arranged in a mosaic pattern in the center of the abdomen. Note the lack of characteristic haustral or valvulae conniventes markings which are typical of obstruction.

external air as the cause of intestinal distention. It was the latter authors' belief that this air was swallowed. Morris, Ivy, and Maddock proposed that the gas in intestinal obstruction, and particularly ileus, is not swallowed but *respired*. It was observed that even without swallowing gas was seen in the stomach, small intestines, and colon following operations, cystoscopy, or intravenous pyelography. With increased respiratory movements, negative intrathoracic pressure, and reflex changing of the tone of the superior esophageal sphincter, air is respired directly into the gastrointestinal tract.

UNUSUAL ABDOMINAL DISEASES DIAGNOSED FROM THE SURVEY FILMS

Congenital bowel obstruction. Congenital anomalies are often the cause of intestinal obstruction. These anomalies are usually encountered in infants and children and may be due to atresia, bands, muscular hypertrophy, or malrotation. The survey films can usually aid in locating the site of obstruction. Not infrequently the exact congenital deformity may be diagnosed. They are of especial value in pyloric stenosis and imperforate anus. In nonrotation of the colon, small bowel loops, particularly ileum, may be noted on the right side of the abdomen and the entire portion of the gas-filled colon located on the left.

Mesenteric vascular occlusion. This intestinal catastrophe composes 2 to 5 per cent of the strangulating obstructions, and the mortality is extremely high. Immediate diagnosis and treatment are necessary. This disorder can be diagnosed occasionally on survey films of the abdomen. The superior mesenteric vessels supply most of the small intestine and the right half of the colon. Occlusion of these vessels may cause a distention of the right half of the large bowel which may end abruptly at the splenic flexure. Observation of this sign on the survey films may permit early diagnosis and treatment.

Volvulus. Volvulus of the sigmoid colon is often diagnosed on the survey films (Fig. 5). The imminence of a ruptured bowel in volvulus demands immediate diagnosis and treatment. Rigler and Lipschultz (7) set forth the criteria for which the radiologist should search when attempting to diagnose volvulus on the survey films. Rigler (6) has re-emphasized that "coffee bean" loops located in the right upper quadrant with thick edematous bowel walls between the adjacent segments are typical of volvulus. Double fluid levels or two points of obstruction may be seen. Volvulus may be differentiated from acute obstruction of a carcinomatous sigmoid colon. The differentiating point is that the large dilated loops of a carcinomatous obstruction do not rise out of the pelvis into the right upper quadrant.

Gallstone obstruction. (Fig. 6). Gallstone obstruction, like mesenteric thrombosis, has a high mortality rate when treatment is delayed. It is sometimes simple to diagnose from the survey films. As gallstone obstruction composes approximately 2 per cent of all bowel obstructions, its presence should at least be suspected when contemplating the survey

Fig. 5. Volvulus of the sigmoid colon. Note the large double loop in the right upper abdominal quadrant.

Fig. 6. Gallstone ileus. Arrows outline a large ring-like biliary calculus in the midportion of the left abdomen.

films. It may be suspected on the film of an obese, middle-aged female. Gas outlining the biliary tract may be seen following the erosion of a gallstone into the stomach or bowel. The roughest stones, and not the largest ones, are the most likely to obstruct, and the ileocecal valve is most often the obstructive site. There is little doubt that the survey films can aid in an early diagnosis of gallstone obstruction and thus lower the high mortality rate of this disorder. Figure 6 demonstrates a large biliary calculus which was diagnosed and later confirmed by operation.

Intussusception. This is an abdominal emergency best diagnosed by retrograde barium studies but may be diagnosed occasionally on the survey films. Levitin's cases were diagnosed from the survey films by the obvious appearance of a loop of ileum invaginated into the cecum. The roentgenologic diagnosis is dependent upon the knowledge of the usual location and the pathologic anatomy of the intussusception. About two-thirds of the intussusceptions are enterocolic. On the survey films gas may stop at the caput and a small triangular intrusion ("bird's beak") may be seen in the central canal. Air may fill the peripheral sheath and give a forked appearance ("pincers'" sign).

Aortic aneurysms. Dissecting aortic aneurysms may cause severe abdominal pain and on the survey film may simulate a perinephritic or psoas abscess. Dissecting abdominal aneurysms, like psoas muscle and perinephritic abscesses, causes an obliteration of the psoas muscle and a dorsolumbar scoliosis with the convexity to the opposite side of the lesion. An aneurysm may be suspected by calcification in an enlarged bulbous abdominal aorta or by a lateral view showing erosion of the vertebral bodies with a sparing of the intervertebral discs.

Pancreatic disease. Pancreatic necrosis may be diagnosed on the survey films by the pathognomonic nodular densities of saponified fats scattered throughout the abdominal cavity. Although acute pancreatitis cannot be definitely diagnosed on the survey films, its

presence can at least be suspected by an increased opacity in the region of the pancreas, the wide separation between the gas shadow of the stomach and colon, a large, flabby, gas-filled duodenal bulb, and linear atelectasis in the base of the left lung. It has been emphasized that any patient with fluid in the left lung base may have pancreatitis.

Ruptured spleen. Despite the characteristic appearance of ruptured spleen on the survey films, only a few cases are reported in the literature. Many of these cases show serrations along the greater border of a hugely dilated stomach and fractures of adjacent ribs.

MULTIPLE AND NEGATIVE FINDINGS ON THE SURVEY FILMS

Numerous other acute abdominal conditions may be deduced from multiple findings. On roentgenograms of a female patient, a pelvic mass with small calcifications may represent a twisted ovarian cystadenoma. A grossly dilated stomach and Charcot's hips may suggest tabetic crises. Fractured vertebrae and sickle cell anemia may cause abdominal crises and the typical bone findings should be searched for on the abdominal roentgenogram. The clinical diagnosis of other conditions such as diabetic and uremic crises, arachnoidism, and coronary occlusion may be further substantiated by a normal survey roentgenogram.

CONCLUSIONS

1. The "survey films" of the abdomen are frequently of great aid in the diagnosis of biliary and renal lithiasis, bowel obstruction, ileus, peritonitis, abscess, and ruptured viscus. Many disorders such as mesenteric thrombosis, splenic rupture, volvulus, gallstone obstruction, intussusception, and congenital bowel obstructions occur uncommonly, but an early diagnosis made from the abdominal studies may give the patient a more favorable chance for recovery.

2. Four roentgenograms are necessary for a complete examination of the abdomen: a high and low supine roentgenogram, an upright roentgenogram, and a posteroanterior chest roentgenogram. Portable studies do not suffice.

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COMPILATION AUTOGRAFTS OF THE SUBCLAVIAN ARTERY FOR BRIDGING SHORT DEFECTS IN THE THORACIC AORTA

An Experimental Study With Pertinent Human Measurements

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THE surgical treatment of coarctation of the aorta is a well established procedure. In some instances, end-to-end approximation of the aortic edges is impossible after excision of the coarctated segment. An alternative method is the division of the left subclavian artery distally, turning the proximal portion down and anastomosing it to the distal aortic segment. The end result is unpredictable and frequently unsatisfactory. Aortic homografts, when available, give immediate satisfactory functional results as has been shown by Gross. Such grafts are not always available. Furthermore, the development of subsequent calcification and degeneration in homografts is discouraging.

The ideal repair would be by means of an autogenous arterial graft isoproportional with the aorta. Such a graft is impossible to obtain clinically in cases of coarctation except in those instances in which the subclavian has attained large proportions.

It would appear that a large caliber autograft compiled of the patient's own arterial tissue would be most advantageous in certain instances in which grafts are necessary. It has been repeatedly demonstrated that ligation and division of the subclavian artery at the beginning of its second portion can be performed with a high degree of safety. It seemed to one of us (K.A.M.) that a tube of similar caliber as the thoracic aorta could be constructed by using the tissues of the subclavian artery by rearranging its composite parts. It would of necessity be of short length and perhaps of limited applicability but adequate where a short length graft would be required. Actually in the experience of others, the majority of cases require relatively short grafts.

This experimental study was undertaken in order to determine the technical feasibility of such a procedure as well as the ultimate fate of such a graft.

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EXPERIMENTAL METHODS

Operative procedure. Sixteen adult mongrel dogs and 3 partially grown puppies, weighing from 7½ to 15 kilograms, were operated upon under nembutal anesthesia and positive pressure respiration, full aseptic technique being used. The left chest was entered through the fourth interspace, the fourth and fifth ribs being divided dorsally. In a few dogs the fifth rib was resected. The left brachial (subclavian) artery and upper thoracic aorta were dissected free of surrounding tissues. The diameter and circumference of the brachial artery and of the aorta, a few millimeters below the ligamentum arteriosum, were determined. The length of the first portion of the brachial artery was also determined. The brachial artery was then removed between clamps from its origin to the origin of the internal mammary artery. The proximal aortic defect was sutured, and the distal vessel ligated. The excised vessel segment was opened longitudinally and if of sufficient length, as previously determined, the ends were coapted (as in rolling a cigarette) and sutured to form a tube. When the length of the vessel was insufficient to allow formation

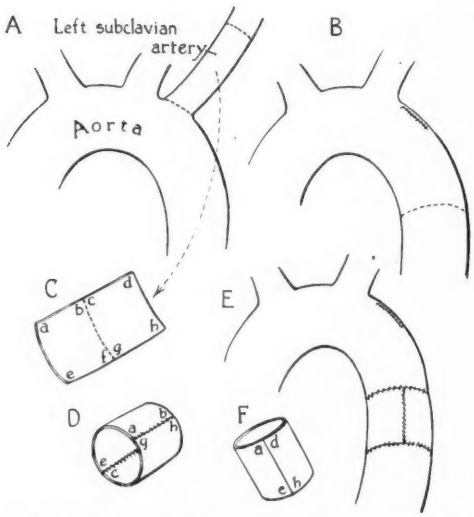


Fig. 1. Diagrams of the steps required to construct an autogenous graft of the subclavian artery. C and D, Illustrations of formation of a 2 piece compilation graft. After removal of the subclavian artery, it is opened longitudinally. This rectangular tissue is now transected into 2 equal squares. These 2 arterial segments are sutured together as indicated. In this fashion a compilation graft is constructed which is half the length but twice the diameter of the original subclavian artery. F, A simpler one piece cigarette construction is shown. The subclavian artery is opened in its longitudinal axis. It is then rolled upon itself much as one would roll a cigarette. Consequently, this graft will have a single suture line. By the utilization of a ruler and caliper for measuring outside diameters, it can be determined readily if the subclavian artery is adequate to bridge the defect and which of the two methods would better suit the situation. This decision can be made before the surgeon is committed to either procedure.

of a tube of adequate diameter by this method, an alternative procedure was used. The subclavian was excised and opened longitudinally as before, then divided transversely into equal halves. The lateral edges of each segment were then sutured together. This gave a tube of larger diameter but of shorter length (Fig. 1). The vessel segments were handled with the utmost gentleness and kept well moistened with physiologic saline at all times. Mineral oil was liberally applied to the vessel and suture during the anastomotic procedure.

Following preparation of the graft, the aorta was divided between Potts clamps and the graft sutured into place. Minimal to moderate bleeding occurred on removal of the clamps. This bleeding was controlled easily in most instances by a short period of light digital pressure. Occasionally, an additional suture was necessary. The length of the graft and the diameter of the graft and adjacent aorta above and below the graft were measured and recorded. The pleura was closed over the aorta, but no additional supporting material was used. The chest wall was closed in layers. Air was aspirated from the pleural cavities after the chest wall closure was completed. Anticoagulants were not used at any time. Penicillin, 300,000 units, was given intramuscularly at the completion of the operation and daily for 3 days thereafter. A full kennel diet was allowed as soon as the recovery from anesthesia was complete.

The diameters of the compiled grafts compared very closely to the aorta in all but 1 case (B-59). Here a "cigarette" type of graft was made and sutured into place even though previous measurement indicated the necessity of a 2 piece graft. Though smaller than the aorta the graft was much larger than the intact subclavian and functioned well until the animal's death from an undetermined cause on the eleventh postoperative day.

One piece grafts were utilized in 7 dogs, and 2 piece grafts were necessary in the remainder. Fifteen dogs died or were sacrificed from 8 hours to 186 days postoperatively.

Ancillary studies. Aortography.—Eight animals surviving over 5 months were subjected to aortography under nembutal anesthesia, 70 per cent diodrast being injected via a polythene tube in a carotid artery.

Measurements.—At the time of operation measurements were made of the length and diameter of the compilation graft in situ as well as the proximal and distal aorta. At autopsy, the thoracic aorta was removed as soon as possible after death. After obstructing each end, the aorta was inflated with air to 120 millimeters of mercury pressure. Measurements of the length and diameter of the graft together with the diameter of the aorta above and below the autograft were made.

Microscopic studies.—Sections for study including the graft were obtained at the suture lines. These tissues were stained with hema-

TABLE I.—MEASUREMENTS OF COMPILED SUBCLAVIAN GRAFTS AT TIME OF IMPLANTATION IN 19 DOGS AND FATE OF THE ANIMALS

Dog	Length of graft, cm.	Diameter of graft, cm.	Diameter of aorta.[1] cm.	Type of graft	Fate of animal
B-51	1.2	0.9	0.9	1 piece (cigarette)	Expired 8 hours postoperatively of pneumothorax
B-46	1.3	1.0	1.1	2 piece	Died on 7th postoperative day of rupture at suture line secondary to abscess
B-58	1.5	1.1	1.1	2 piece	Paraplegic. Sacrificed 12th postoperative day after aortogram revealed good channel. Graft well healed
E-73	1.75	1.1	1.15	1 piece	Died of pneumonia on 13th postoperative day. Graft well healed
B-48	0.75	0.8	0.8	2 piece	Died on 5th postoperative day of massive pleural effusion. Graft open and healing
B-43	0.8	0.9	0.9	2 piece	Died on first postoperative day due to aspiration of food
B-60	1.5	1.05	1.1	1 piece (cigarette)	Died on 14th day of distemper. Graft open and healing. Small plaque of thrombus on wall
B-56	2.0	0.7	0.8	2 piece	Died 3 hours postoperatively after cardiac resuscitation during surgery
B-57	1.0	1.1	1.2	2 piece	Sacrificed on 173rd postoperative day. Aortogram taken. Graft healed. No constriction (Figs. 3 and 5)
B-55	1.0	0.8	0.8	2 piece	Sacrificed on 173rd postoperative day. Graft healed and showed no dilatation or constriction
B-54	0.9	0.8	0.9	2 piece	Died on 7th postoperative day of empyema. Graft open and healing
E-77	1.2	0.8	0.85	1 piece (cigarette)	Aortogram made on 172nd day showed excellent lumen. Still alive
E-80	1.3	0.8	0.8	1 piece	Aortogram made on 172nd postoperative day showed excellent lumen. Still alive
B-61	1.2	0.85	0.8	2 piece	Aortogram on 173rd postoperative day showed excellent lumen. Still alive
B-64	1.0	1.05	0.9	2 piece	Aortogram on 172nd postoperative day revealed excellent lumen. Still alive
B-63	1.5	1.0	0.95	1 piece (cigarette)	Paraplegic after surgery. Sacrificed on 7th postoperative day. Graft open and healing
B-65	1.1	1.0	1.0	2 piece	Aortogram on 171st postoperative day showed excellent lumen. Died on 186th postoperative day. Graft excellent (Fig. 4)
B-67	1.2	1.0	1.0	2 piece	Died of iodine reaction after aortogram 163 days postoperatively. Weight doubled. Graft grew with aorta, no constriction or dilatation
B-59	1.2	1.2	0.67 upper, 0.55 lower	1 piece	Died on 11th postoperative day of undetermined cause. Graft open

[1]At operation the aorta was transected, therefore, both ends are of equal diameter.

toxylin and eosin and in some instances by Weigert's elastic tissue stain.

Studies on fresh human cadavers. From routine autopsy material, 22 patients were studied in order to determine the practicability of the clinical application of these procedures based upon the experimental data. No patient studied had died of coarctation of the aorta. The material consisted mainly of individuals with an average age of 60 years. The length and circumference of left subclavian artery and circumference of aorta at ligamentum arteriosum were determined.

EXPERIMENTAL RESULTS

The lengths, diameters, and end results of the compiled grafts and their recipient aortas in the experimental animals are given in Table I. A comparison of pertinent measurements at the time of operation and at autopsy in 6 dogs on which both sets of measurements were made is contained in Table II.

Eleven dogs died or were sacrificed during the first 2 weeks after graft implantation (Fig. 2). In only 1 animal (B-46) death occurred on the seventh postoperative day due to rupture of a suture line secondary to an abscess formation about the graft. One other dog (B-60) died of distemper on the fourteenth postoperative day, and at autopsy a small plaque of thrombus was found attached to the wall of the graft. This thrombus was small, nonoccluding, and firmly attached to the intimal surface. No other thrombus was noted.

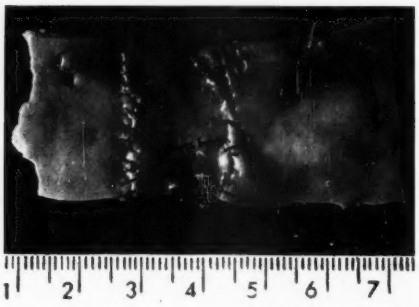


Fig. 2. Dog E-73. Opened specimen, thirteenth postoperative day. Note advanced healing and lack of thrombus formation.

Eight dogs survived for 166 days or longer. In these animals autography was performed. Two dogs were sacrificed following aortography and 2 died shortly thereafter. In every instance a fully patent graft of excellent caliber was noted. In most of these, careful inspection of the x-ray film was required to locate the site of the graft (Fig. 3).

One animal (B-67), a half-grown pup at the time of operation, had doubled its weight. The aorta had increased 69 per cent in diameter and the graft had increased 64 per cent in diameter at the time of death, 166 days later (Fig. 4). Four dogs are being maintained for long term study.

The grafts were found to grossly resemble the aorta. The wall was thickened, the elasticity of the graft was excellent, and there was no gross evidence of calcification or degeneration of the tissue. In all animals, the grafts were found to be patent. In those animals with short survival periods healing was usually well advanced by the first week and appeared to be nearly complete at the end of the second week.

Animals surviving over 5 months revealed that all elements of the graft wall had survived and complete histologic integrity was maintained. The thickness of the media was found to be approximately one-half that of the recipient aorta. The thickening which was present had occurred in the adventitia. The intimal surface was smooth and revealed no abnormality. The suture lines were well healed and only a thin zone of fibrous tissue at the point of approximation was observed. Elastic and muscle fibers were normal in appearance (Fig. 5). The architecture of the transposed vessel segments appeared to be unchanged. Degenerative changes were conspicuously lacking. This is in direct contrast to the calcification, medial degeneration, and fibrosis so frequently seen in experimental arterial homografts and noted also clinically. Since, in making cigarette grafts, a cross section is placed in the longitudinal axis of the vessel wall, some changes might have been expected. Such changes do not seem to have occurred.

TABLE II.—A COMPARISON OF MEASUREMENTS OF GRAFT AND RECIPIENT AORTA AT OPERATION AND AT AUTOPSY IN 6 DOGS

	Length of graft, cm.	Diameter of graft, cm.	Diameter of aorta, cm.	No. days post-operative
B-58				
Operation	1.5	1.3	1.3	
Autopsy	1.5	1.3	1.3	12
B-60				
Operation	1.5	1.05	1.1	
Autopsy	1.5	1.1	1.15	14
B-57				
Operation	1.0	1.1	1.2	
Autopsy	1.2	1.2	1.2	173
B-55				
Operation	1.0	0.8	0.8	
Autopsy	1.0	0.85	0.9	173
B-67				
Operation	1.2	1.0	1.0	
Autopsy	1.3	1.64	1.6	163
B-65				
Operation	1.1	1.0	1.0	
Autopsy	1.38	1.3	1.3	186

Measurements of the length and circumference of the first portion of the left subclavian artery and the circumference of the thoracic aorta at the level of the ligamentum arteriosum were made in 22 fresh cadavers. This information is summarized in Table III.

It is apparent from these measurements that the circumference of the subclavian artery is approximately one-half the circumference of the aorta at the ligamentum arteriosum. Consequently, the manufacture of a 2 piece compilation graft will result in a circumference almost identical to the aorta at this level. The length of the subclavian from the aorta to the take-off of the first branch varies from 3.0 to 4.4 centimeters; therefore, one could anticipate an autograft of 1.5 to 2.2 centimeters long (Fig. 6). It is apparent also that if a cigarette graft were contemplated, a

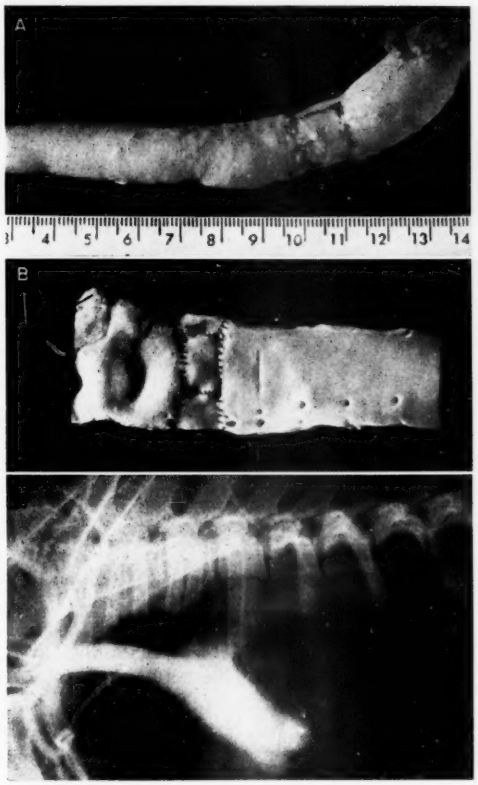


Fig. 3. Dog B-57, 173 days postoperative; 2 piece compilation graft. A, Autopsy specimen inflated to 120 millimeters of mercury. The graft is of normal appearance, texture, and elasticity. B, Opened specimen revealing clean suture lines with good healing. C, Aortogram taken prior to sacrifice. The caliber of the graft and aorta is so similar that it is impossible to locate on the roentgenogram the graft which was implanted at the level of the ligamentum arteriosum.

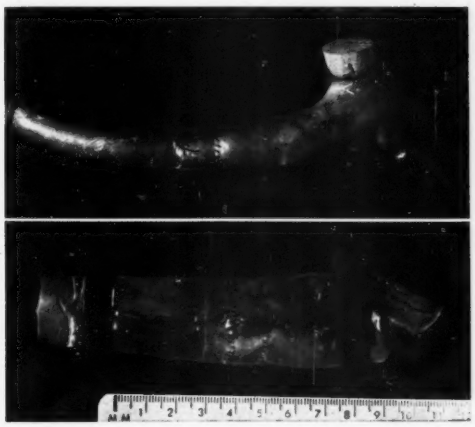


Fig. 4. Dog B-67. Intact and open view, 163 days after implantation of a 2 piece compilation subclavian graft into the thoracic aorta. This young dog following implantation matured and gained 100 per cent in weight. The graft grew at a rate equal to that of the recipient aorta. Length of graft at implantation: 1.2 centimeters; at autopsy: 1.3 centimeters; diameter of graft at implantation: 1.0 centimeters; at autopsy: 1.64 centimeters; diameter of aorta at implantation: 1.0 centimeters; at autopsy: 1.6 centimeters.

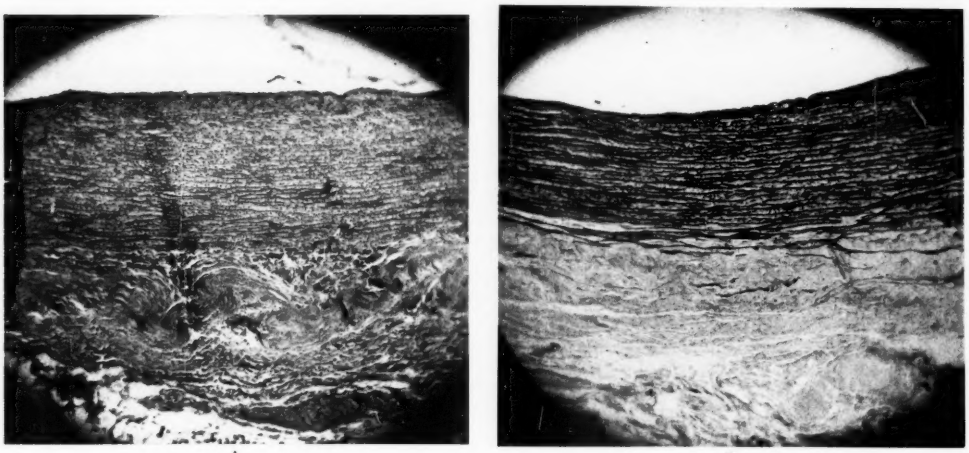
somewhat greater length could be obtained. However, the circumference and consequently the diameter would be smaller than that of the aorta. Nevertheless, the tube formed would be larger than a turned down subclavian.

DISCUSSION

Hurwitt has used a compilation graft of splenic artery to bridge defects in the abdominal aorta of dogs, and Harkins and associates have performed experiments with various types of fresh and preserved compilation and composite grafts in growing pigs. Johnson has described a method that he used clinically in which a narrowed proximal aortic segment was divided longitudinally as was the first portion of the left subclavian artery and the incised edges sutured together to form an adequate vessel.

The use of a graft of some sort is a necessity in a small portion of coarctation operations if a hemodynamically satisfactory result is to be obtained. An autogenous graft is preferable to a homologous graft because it produces no antigenic reaction. Additional disadvantages of the homologous graft are its lack of ready availability, difficulties of preservation, relatively short storage life, and uncertainty as to the eventual fate of homografts in the body.

Uncompiled subclavian arterial grafts either as free grafts or as "turn downs" are usually much smaller in diameter than the aorta and may still leave a relative coarctation with only partially satisfactory results both functionally and hemodynamically. Venous autografts have been used experimentally in the aorta



A B

Fig. 5. Dog B-57. Photomicrographs of graft, 173 days after implantation. A, Cross section; hematoxylin and eosin stain. ×30. B, Same specimen, Weigert's elastic tissue stain. ×30.

and have not proved satisfactory because of the high incidence of early failure and later dilatation.

The compiled subclavian arterial autograft has the disadvantage of short length, and multiplicity of suture lines with their associated danger of dehiscence and thrombus formation. The danger of subclavian interruption though uncommon must be considered.

In favor of the subclavian compilation grafts where only short defects must be bridged are ready availability in the operative area of the necessary material, viability, and autogenicity. If a 2 piece compilation graft is used, the aortic caliber can be matched almost perfectly. The graft length will be equal to half of the length of the subclavian artery. With a single piece, cigarette roll graft, the length of the graft will be equal to the original circumference of the subclavian artery; the reformed circumference will be dependent upon the original length of the vessel. This results in a tube with a caliber less than that of the aorta but superior to a turned down intact subclavian. The average increase in circumference of the cigarette roll graft over a turned down subclavian varies from 0.10 to 2.25 centimeters the average being 1.12 centimeters. While this would not appear to be great, in terms of volume flow[1] it could mean the difference between a satisfactory versus an unsatisfactory result.

Fig. 6. Two piece compilation subclavian autograft implanted into the aorta of a human cadaver at autopsy. Specimen inflated to 120 millimeters of mercury pressure with air. Note excellent matching of calibers. Graft measured 2.4 centimeters in length.

The importance of an increased diameter in terms of volume flow can be readily shown. The human measurements recorded are in terms of circumference. There is a direct correlation between circumference and di-

[1]Poiseuille's law.—The pressure head remaining constant, then the velocity is directly proportional to the sectional area of the tube, but the quantity of fluid passing through the tube per unit of time (volume flow) is proportional to the fourth power of the diameter of the tube.

TABLE III.—MEASUREMENTS OF LEFT SUBCLAVIAN ARTERY AND AORTA AND OF SUBCLAVIAN COMPILATION GRAFTS IN 22 FRESH HUMAN CADAVERS

	A. Left subclavian artery and aorta				B. Subclavian compilation grafts computed from actual measurements			
Cadaver	Length of subclavian[2] from its origin to the origin of:		Circumference[1] of midportion of the subclavian artery, cm.	Circumference[1] of aorta at ligamentum arteriosum, cm.	Maximum circumference possible with 2 piece compilation graft[3], cm.	Maximum length of 2 piece compilation graft[4], cm.	Maximum circumference possible with 1 piece cigarette compilation graft[5], cm.	Maximum length of 1 piece cigarette compilation graft[6], cm.
	Vertebral artery, cm.	Thyrocervical trunk, cm.						
1	3.2	4.5	3.75	6.2	7.5	2.25	4.5	3.75
2	4.0	4.1	3.7	5.4	7.4	2.05	4.1	3.7
3	3.8	4.3	3.45	7.8	6.9	2.15	4.3	3.45
4	3.7	4.4	3.15	7.1	6.3	2.2	4.4	3.15
5	3.5	4.0	3.5	7.8	7.0	2.0	4.0	3.5
6	3.6	4.3	3.45	7.5	6.9	2.15	4.3	3.45
7	4.4	5.3	3.5	7.4	7.0	2.65	5.3	3.5
8	3.8	4.4	3.4	6.3	6.8	2.2	4.4	3.4
9	3.7	4.1	3.4	6.4	6.8	2.05	4.1	3.4
10	5.3	6.0	3.75	8.3	7.5	3.0	6.0	3.75
11	4.0	4.0	2.8	5.6	5.6	2.0	4.0	2.8
12	3.7	3.8	2.9	6.0	5.8	1.9	3.8	2.9
13	arose from aorta	4.2	2.5	5.2	5.0	2.1	4.2	2.5
14	4.0	4.4	3.45	6.0	6.9	2.2	4.4	3.45
15	4.0	5.0	3.5	6.6	7.0	2.5	5.0	3.5
16	4.0	4.6	2.8	6.0	5.6	2.3	4.6	2.8
17	3.0	3.8	2.85	6.5	5.7	1.9	3.8	2.85
18	3.6	4.4	2.5	5.5	5.0	2.2	4.4	2.5
19	4.0	4.1	3.45	7.5	6.9	2.05	4.1	3.45
20	4.0	4.6	2.85	6.0	5.7	2.3	4.6	2.85
21	3.7	4.2	3.4	5.9	6.8	2.1	4.2	3.4
22	3.1	3.5	3.4	6.2	6.8	1.75	3.5	3.4
Average	3.86	4.36	3.25	6.51	6.5	2.18	4.36	3.25

[1]The circumference referred to was considered to be the diameter of the flattened, unstretched, empty vessel × 2.
[2]The length of the subclavian was considered to be the distance from its origin to the thyrocervical trunk.
[3]The maximum circumference would be double the circumference of the intact subclavian artery.
[4]The maximum length is half of the original length of the intact subclavian artery.
[5]The maximum circumference would be the length of the intact subclavian.
[6]The maximum length would be the circumference of the intact subclavian.

ameter. By manipulating the formula for computing circumference ($C = 2\pi r$) this factor can be established:

$$C = 2\pi r = \pi D \text{ or } D = \frac{C}{\pi}$$

In evaluating the relative merits of the intact turned down subclavian artery and the 1 piece cigarette graft, it is possible to establish a ratio with regard to volume flow between the two. The average circumference of the intact subclavian artery is 3.25 centimeters; the average circumference of the cigarette graft is 4.36 centimeters. According to Poiseuille's law the volume flow is directly proportional to the fourth power of the diameter. Therefore, utilizing the average values already given a ratio can be computed:

$$\frac{VF}{VF'} = \frac{D^4}{D'^4} = \frac{\left(\frac{C^4}{\pi}\right)}{\left(\frac{C^1}{\pi}\right)}4 = \frac{C^4}{C'^4} = \frac{(3.25)^4}{(4.36)^4} = \frac{111.57}{358.89}$$

Therefore, on the average, a cigarette graft of the subclavian artery allows an approxi-

mate increase of 320 per cent in volume flow over a turned down intact subclavian. Such a calculation can be readily made for each individual case. Another factor also influencing the choice would be the length needed. By utilizing a cigarette graft rather than the intact subclavian approximately a centimeter in length would be lost. However, in terms of circumference alone and consequently volume flow, in each individual instance the cigarette graft theoretically proved to be superior.

As indicated previously, by the utilization of a ruler and a caliper for measuring outside diameters, one may readily establish the merits of each method involving the subclavian artery; viz., the 2 piece compilation graft, the cigarette roll, and the turn down graft. Therefore, in the individual case the procedure which gives promise of yielding the best result can be predetermined before the surgeon commits himself operatively.

CONCLUSIONS

1. The subclavian artery is a readily available source of autogenous arterial tissue which can easily be compiled or rolled into a tube of adequate diameter to repair defects of short length in the thoracic aorta in the dog.

2. These grafts remain patent and function satisfactorily for periods up to 6 months.

3. These grafts do not undergo degenerative changes during this period of time. Histologic integrity is maintained.

4. Growth of such grafts occurs and keeps pace with growth of the recipient aorta.

5. Pertinent measurements in the human cadaver at autopsy indicate that the experimental work herein reported is applicable clinically.

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INTRAGASTRIC TEMPERATURE: ITS VARIATIONS IN GASTRIC ULCERS

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THE temperature of an area of the body or an organ must be looked upon as being variable. Regional temperature is dependent upon rate of blood flow, oxygen consumption, and heat gained or lost through outside influences. The emotional state of the individual by causing sweating or blushing has a direct bearing on regional temperature, as the local vascular response is regulated by nervous impulses. Emotional states are reflected in the vascular blushing of the gastrointestinal mucosa.

It is often assumed that emotional states, coming as but small repeated taps on an already overburdened nervous system, due perhaps in part to heredity, may be looked upon as being a subtle form of trauma which, over a period of time, produces the same effect as actual violent injury. The nature of the response and the time required for the vascular system to respond to the trauma depends upon the degree and nature of the injury. A skin burn or a blow results in a regional dilation of the blood vessels as a direct result of the local chemical tissue change. This local reaction may be accompanied by reflex reactions in the opposite direction of other blood vessels at one or more other regions of the body, as was originally pointed out by Loven. On the other hand, deep injury often results in a local vasospasm and a general response of deep shock with its associated vasodilation and bradycardia.

Tissue respiration is directly dependent upon blood flow. It is therefore important to think of the body architecture as physiologic anatomy. In the light of rational and conservative body response, the blood requirements of an organ or tissue at rest would not be equal to the requirements of the same structure during different degrees of activity. It becomes obvious that shunting or by-passing should be a normal physiologic phenomenon. Blood is diverted to the tissue or organ with the greatest need.

Since a change in temperature follows upon any regional change in blood flow, and therefore oxygen exchange, experiments were devised to demonstrate the relationship between the vascular pattern and intragastric temperatures. In this connection, it might be stated that, according to Kottke, hypoxia decreased the ability of men to control body temperature and, with the inhibition of shivering, favored greater heat dissipation in men. Hypoxia causes hypoxemia, and this in turn leads to anoxia of a greater or lesser extent in areas activated regionally because of body demands. The composite individual is the best example of division of labor. Each organ or tissue is dependent upon each other tissue or organ for its very existence. In the normally functioning individual numerous episodes of autotransfusions from tissue to tissue and organ to organ take place for the purpose of tissue metabolism. The factors in heat dispersion in the blood vessels of animals and men were first described by Claude Bernard and evaluated in a more satisfactory manner by Krogh. Bazett, Love, Eisenberg, Day, and Forster, advanced our present knowledge of temperature changes in the blood vessels of man. It seemed reasonable to suppose, therefore, that if the blood volume and rate of flow to an area were increased, the temperature would follow suit, and that conversely, if the blood volume and rate of flow were reduced, the temperature in the area would fall.

MATERIALS AND METHODS

For this study we made a thermopile of iron constantan wires threaded through a poly-

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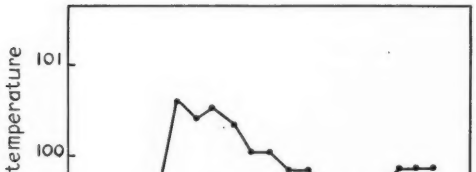

Fig. 1. Graph made from a continuous recording potentiometer. The graph shows the gastric temperature excursions during the noon hour in a normal male. The oral temperature remained at 98.4 F.

vinyl plastic tube. This thermopile was made up of 8 thermocouples, separately insulated. The thermopile was conducted to a fixed cold junction in a thermos bottle. Although these elements were insulated, they were immersed in an ice bath of distilled water. The thermos bottle was grounded and the thermopile was connected by 2 well insulated leads to a specially constructed potentiometer with a 10 degree range and a 24 hour automatic recorder. The 24 hour automatic recording was instituted to obviate errors by a nurse in attendance unfamiliar with galvanometric readings. The reason for the use of a thermopile instead of a single thermocouple was to reduce the percentage of error by increasing the total electromotive force. The resultant electromotive force was the total of the electromotive forces of the 8 couples. Great difficulty was experienced in attempts made to pass the thermopile from the cardiac-fundic area to the pyloric area. The thermopile would curl and re-enter the esophagus. We constructed a new pile. Gum rubber tubing was used as the sheath. The tips of the individual thermocouples were insulated with "sauereisen" and then covered with a rubber plastic. To the end of the plastic tip a rubber balloon containing 5 cubic centimeters of mercury was anchored. The entire assembly was then passed through the nares. The weight of the mercury carried the termopile into the stomach with little effort on the part of the patient. The patient was then rolled on his right side and the weighted ballon rode the crest of the spinal column and fell into the pyloric end of the stomach, carrying with it the tip of the thermopile(2).

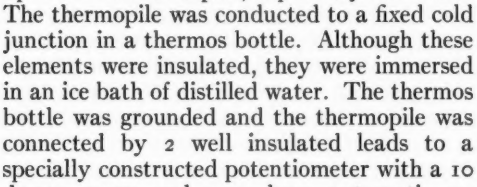

Fig. 2. Graph made from the continuous recording potentiometer. This graph demonstrates the fall in intragastric temperature during the hunger contraction phase in the normal male. When hunger contractions stopped the intragastric temperature began to climb. The oral temperature taken with a clinical thermometer remained at 98.6 F. throughout the entire experiment.

In animal experimentation a bead type thermistor was fixed in an intravenous catheter and passed into the heart as well as into the abdominal aorta to the level of the celiac axis. Laboratory made thermistors are best in experimental work, as they may be developed for the exact task contemplated. These thermistors were made of platinum alloy. They were sweated together by placing the two wires parallel to each other, held in position by small thyroid clamps, and then soldered together with a high grade solder. The fused wires were drawn through a narrow gauge lead-free glass tubing. The tubing was spot heated and drawn out so that a bead of glass was welded to the fused wires and the excess glass was flamed off at each end, sealing the point of contact. The leads were covered with insulating varnish and both wires coated with plastic of high non-wetting surface. This was done to avoid venous thrombosis or thrombus formation within the right auricle of the heart. The thermistor was passed through the left carotid artery into the descending thoracic aorta or through the right

carotid into the left ventricle. If it was desirable to ascertain the temperature of the right heart, the thermistor was passed through the right basilic vein. In using a vein, a regular venous cannula was employed. The thermistor was threaded through this needle after the obturator was removed; whereas, when an artery was used, the thermistor was threaded directly into the artery through an inverted V incision and its passage observed under fluoroscopy. When the desired area was reached, the thermistor was tied in place. When it was necessary to obtain the temperature of the free flowing blood at the level of the stomach, the left common iliac artery was entered using the same technique as when the carotids were used. This was done through a laparotomy incision so that the position of the thermopile and thermistor would be checked by direct palpation. These temperatures were used as the base body temperature as compared to the gastric temperatures taken with the thermopile.

The thermopile was passed through an esophagostomy opening into the stomachs of anesthetized dogs. The thermistor was passed through the right median basilic vein into the right heart and constants or standards taken. The thermopile was left at first in the cardiac-fundic area. It was later moved to the pyloric area. In man, the thermopile was left 12 hours in the cardiac-fundic area and the same length of time in the pyloric region. The temperature in the pylorus was found to be 2 degrees higher than in the cardiac-fundic area when constants were taken and no surgery or stimulation had been done. The thermopile was also passed into the stomach of patients with known gastric or duodenal ulcers as proved by surgery. The nose was used as the portal of entry. Oral temperatures as well as rectal, by means of a clinical thermometer, served as controls. The temperatures of the rectum, the cardiac-fundic area, and the pylorus of the stomach may all differ considerably. The magnitude of the temperature excursions varies directly as the blood flow and oxygen consumption of the region.

The thermopile, as stated, was passed through the nose. The tubing was well lubricated and the patient was directed to swallow.

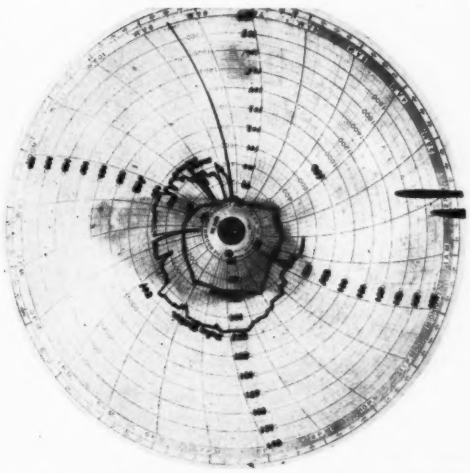

Fig. 3. This male adult's entrance complaint was gastric bleeding. The patient had numerous transfusions of citrated blood. The temperature recording began at 8:15 a.m., 24 hours after all bleeding had stopped. The intragastric temperatures ranged from 98 to 101.8 degrees F. The oral temperatures reached a height of 100 degrees F. The lowest oral temperature was 98 degrees F. The highest gastric temperature was not associated with the highest oral temperature. This graph shows the diurnal and nocturnal hunger cascade.

To avoid regurgitating the tube, he was instructed to breathe rapidly through his mouth before each swallowing effort. The position of the tip of the thermopile was checked by fluoroscopy. The tube in place, the leads were attached to the potentiometer. The temperature of the cold junction was checked and the potentiometer was activated. A zero or static fix was made by racking the indicator back and

TABLE I.—TEMPERATURES, ORAL AND INTRAGASTRIC IN NORMAL MALES (EXPRESSED IN DEGREES FAHRENHEIT)

Subject	Oral temperature	Initial intragastric temperature	Hunger phase intragastric temperature
1	98.6	101.0	98.8
2	98.8	100.6	99.4
3	98.6	99.8	98.8
4	97.8	100.0	99.2
5	98.6	100.6	99.2
6	98.2	100.7	100.2
7	98.0	101.0	99.3
8	97.8	100.0	99.0

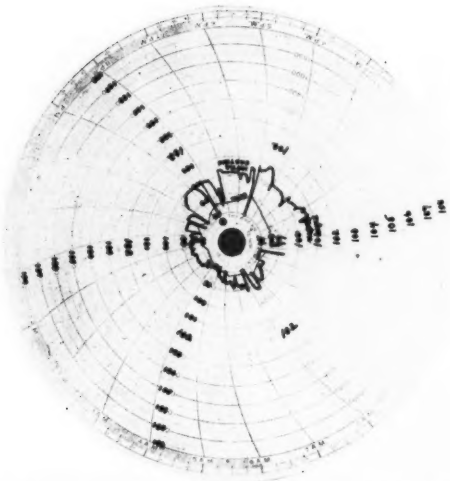

Fig. 4. This is a photograph of a graph showing a 24 hour recording of the intragastric temperature. The oral temperatures were plotted in from the nurses' records. This patient had a prepyloric ulcer and entered with a complaint of pain. Bleeding was not a feature of this case. His recordings began at 1:30 p.m. and ended at 11:40 the next morning. Highest intragastric temperature was 100.9 degrees F. Highest oral temperature was 99 degrees F. Lowest gastric temperature was 98 degrees F. and the lowest oral temperature was 97.6 degrees F. The first hunger cascade took place at 5:00 p.m. The erratic curve was associated with restlessness and hunger.

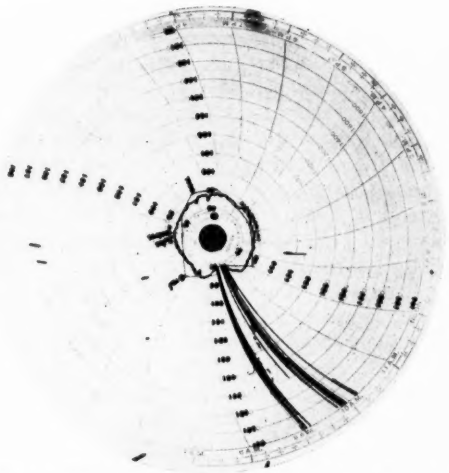

Fig. 5. This graph is highly instructive as well as interesting. This patient had a sleeve resection, followed by a subtotal gastric resection. Because of continued complaints a transthoracic vagal neurectomy was done. At his entrance, he complained of pain and abdominal distress. He was a known tabetic and was now in crisis. His highest gastric temperature was recorded as 98.8 degrees F. His highest oral temperature was 99 degrees F. Note the absence of cascading. Neither peaks nor troughs are demonstrated. This graph is so constant that it could almost be copied by means of a stationary stylus registering on a spinning drum.

forth until it came to rest and stopped wandering. The moment the switch for the racking was released, the inked stylus automatically recorded on a circular rotating chart. The oral and rectal temperatures were taken periodically and charted.

Numerous patients were used to get intragastric temperatures. Our normal subjects were male and female first year medical students of Marquette University School of Medicine. Our other patients were all males who had gastric ulcers (4,5). These ulcers were prepyloric. Some of these patients entered the hospital for definitive treatment because of recurrent episodes of pain. Some entered in a state of shock because of prolonged slow bleeding, while others were brought in because of a massive hemorrhage followed by collapse. Two patients were so ill that they were put on the critical list. They were cold, pallorous, and clammy. The pulse was weak, thin, and thready. These patients were repeatedly transfused and, when they had sufficiently improved and all bleeding had stopped, intragastric temperatures were taken. One patient had a subtotal gastric resection. Two years prior, he had had a sleeve resection of the pyloric area. As his complaints persisted and because of massive intra-abdominal adhesions, a transthoracic vagal neurectomy was done. He felt well for a short period of time and then returned to the hospital because of numerous abdominal complaints.

Some of the patients were obese, but the majority were thin. The nurses took the temperatures as requested and made elaborate notes of their own observations and of the complaints made by each patient. All our subjects were instructed to inform the nurse of any and all complaints. They were asked to register immediately all prodromal symptoms of hunger, pain, restlessness, or bleeding. All of the patients were found to be quite cooperative.

CLINICAL FINDINGS

In our normal subjects, as is noted in Table I, the oral temperatures consistently ran 1 to 3 degrees lower than the intragastric temperatures. In our experiments, as shown in the curves in Figures 1 and 2, it was noted that approximately ½ hour following the patient's desire for food, the temperature took a sharp dip to a lower level and shortly thereafter became elevated to its previous or near previous plateau, after the subject's "hunger pangs" had subsided.

In the ulcer subjects, the following cases epitomize our findings:

CASE 1. This patient, a male adult, entered the hospital because of gastric bleeding. He regurgitated frank blood and coffeeground material. His stools had been melenic for a few days, but he had not thought much of his experience until he had an episode of frank hemorrhage. The patient was repeatedly transfused with citrated blood and the temperature recordings were done following a 24 hour period of bleeding. The thermopile was passed with great ease, as the patient had considerable experience with tube feedings and test meals. The recordings began at 8:15 a.m. and ended at 2:00 a.m. the next day. The lowest temperature recorded within the stomach was 98 degrees F. and the highest was 101 degrees F. His graph, seen in Figure 3, shows the drop in temperature. This drop followed shortly after his desire for food was expressed.

CASE 2. This patient entered the hospital with a complaint of abdominal pain. This pain was no longer eased by the ingestion of food. Antacids gave him some relief but the episodes of night vomiting disturbed his sleep so much that he was unable to work the following day. He did not bleed at any time. This male was well developed and well nourished. His diagnosis was prepyloric ulcer. His temperature recordings began at 1:30 p.m. and ended at 11:40 the next morning. The highest intragastric temperature was 100 degrees F. and his highest oral temperature was 99 degrees F. His lowest intragastric temperature was 98 degrees F. The first drop associated with hunger took place at 5:00 p.m. From 7:00 p.m. until the tube was removed, he was restless and hungry. The graph shows a rather erratic intragastric temperature curve. The oral temperatures were more static and corresponded to the diurnal and nocturnal variations normally expected. The photograph of this graph is shown in Figure 4.

CASE 3. This case was especially interesting and instructive as well as unusual. He had numerous previous admissions to different hospitals. His surgical experiences included a sleeve gastric resection. Because of persistent pain and discomfort, he had a transthoracic vagal neurectomy. This was followed by a short period of comfort. He entered the hospital this time because of a veritable crescendo of symptoms. It is of great import to note that this patient was a known luetic and at times had been diagnosed as in tabetic crisis. His highest intragastric temperature was recorded as 98 degrees F. and his highest oral temperature was 99 degrees F. His highest oral did not coincide with his highest intragastric temperature. Peaks and troughs like those seen on the usual ulcer graphs were not present. As this patient had learned to eat small quantities of food almost constantly, he did not give voice to fixed periods of hunger. This was reflected in his graph. His entire graph of intragastric temperatures was charted in a 1 degree range, varying between 98 and 99 degrees F. (Fig. 5).

Temperatures were recorded from numerous other ulcer patients. The temperature variations were apparently related to the degree of activity of the ulcer. Activity of an ulcer, as previously stated, is always associated with hyperactivity of the stomach as well as hypersecretion and, as activity is always attended by increased blood flow and oxygen consumption, the temperature must of necessity follow suit.

SUMMARY

Physiologists and anatomists have demonstrated that the simple mammalian stomach is divided into two essential parts, the line of demarcation being the incisuria angularis. Of course, such a point of view depends upon the observer's perspective. Anatomically, the stomach is described as the largest dilatation of the digestive tube, connected at the cephalic end with the esophagus, and at the caudal end with the beginning of the small intestine. Histologically, the stomach may be divided into three parts on the basis of epithelium structure and glandular arrangement. For our purpose, we divided the stomach into two regions on the basis of the temperatures recorded.

It was noticed, in the experiments performed on our subjects with the intragastric thermopile, that approximately ½ hour following the patient's desire for food, the temperature took a sharp dip to a lower level and shortly thereafter became elevated to its previous or near previous plateau, as in Figures 1 and 2. It was believed that this reaction took place because the muscular contractions of the stomach arrested the blood flow and led to a

dearth of oxygen and a reduction of regional metabolism. This contention is based on the previously published work done at this institution on the neurovascular mechanism of the stomach (3–5), where it has been demonstrated that in the stimulated stomach, the mucous membrane is kept in a state of anemia because of the shunting mechanism of the vascular bed.

Christensen(7), by use of the plethysmographic method and skin thermocouples, showed that there was a considerable reduction of the blood flow in the skin at the beginning of exertion. The initial constriction of the skin vessels gives way in a few minutes to vasodilation. This serves as a heat regulating mechanism. His experiments showed that at the start of heavy work there is an instantaneous and vigorous reduction in the finger bloodflow. This lasts several minutes. It is a regulatory phenomenon for the adjustment of the circulation at the transition point from rest to work. He felt that the response was too sudden to be motivated by hormonal adrenal secretion.

Christensen's(8) results in his skin experiments so closely paralleled the findings in present work on the stomach that the only logical conclusion was that the phenomena were the same. The change in temperatures associated with the prodromal symptoms of hunger repeated itself in numerous graphs made from the studies of different subjects. This has been a study of the gastric temperature response to gastric ulcers and hunger contractions. A major difficulty was the development of adequate equipment for taking regional temperatures within the esophagus, cardiac-fundic area, and pylorus, and for recording these automatically over a 24 hour period. The problem of moving the thermopile from place to place within the stomach was solved by the use of a weighted balloon attached to the tip of the jacketed thermopile.

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BLOOD VOLUME STUDIES IN NORMAL HUMANS

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VARIOUS methods have been utilized for the determinations of plasma and total blood volumes. Most have depended upon the dilution by the blood stream of some introduced material, such as foreign proteins, vital dyes, gum acacia, radioactive iron, chromium, or phosphorus labeled red cells, or iodinated (I^{131}) human serum albumin.

Since it is impossible to measure directly the plasma and blood volumes in a series of normal individuals, there are no absolute values available for determining the accuracy of any given indirect method. On the other hand there are certain theoretical and practical considerations which justified the prediction that the various methods outlined would yield different "normal values." Experience has borne out this prediction but it was believed that further study was indicated to compare the results obtained by some of these methods of plasma and blood volume determination.

The study was divided into three parts. Part I dealt with the determination of the plasma and blood volumes utilizing iodinated (I^{131}) human serum albumin. Its purpose was to compare the plasma volume obtained by extrapolation of the observed disappearance curve of the material from the blood stream to the time of injection, with the plasma volume obtained from the activity of a single, 10 minute sample withdrawal. Part II was designed to compare the Evans blue dye method and the iodinated human serum albumin method from the standpoint of reproducibility of results. Serial determinations of plasma volumes were performed on normal individuals divided into two groups, by using consistently one method for each group. In Part III the plasma and total blood volumes were compared in a group of normal humans as determined simultaneously by using radioactive phosphorus tagged red blood cells, iodinated human serum albumin, and Evans' blue.

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The opinions expressed herein are those of the authors and not necessarily those of the Department of the Navy.

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PART I: ONE SAMPLE WITHDRAWAL VERSUS THREE SAMPLE WITHDRAWAL

Fine and Seligman in 1943 reported the use of iodinated human serum albumin to determine the plasma and total blood volumes. Storaasli and associates have also evaluated the use of this material in the determination of plasma and total blood volumes.

It was the purpose of this investigation to determine whether the plasma volume calculated from the activity of 1 sample of blood withdrawn 10 minutes following the injection of a predetermined amount of iodinated (I^{131}) human serum albumin was comparable to that obtained by using the activity obtained by extrapolation to the time of injection from the disappearance curve of the material from the blood stream.

Selection of patients. Subjects were patients admitted for elective surgery to the surgical wards of the U. S. Naval Hospital, Bethesda, Maryland, and corpsmen volunteers attached to the National Naval Medical Center, Bethesda, Maryland. Twenty subjects were studied by each of the two methods.

Methods. Each patient or subject received approximately 50 microcuries of iodinated (I^{131}) human serum albumin intravenously in one arm. With the first group of patients one sample of blood was withdrawn without stasis, 10 minutes later from the other arm, by the use of heparinized syringes. With the second group of patients 3 samples were withdrawn without stasis, approximately 10, 20, and 30

minutes after the time of injection. All withdrawn samples were put in heparinized tubes.

A hematocrit was performed on each sample. The values were averaged and corrected by the factor of 0.96 to account for the plasma trapped among the packed cells. The remainder of each sample was centrifuged at 3,000 revolutions per minute for 30 minutes. Duplicate 2 milliliter specimens were counted from each sample by means of a mica end-window Geiger tube. Duplicate 2 milliliter samples of a check solution, prepared from the same solution used for the dose and diluted 1:100 with nonradioactive plasma, were counted in the same manner.

In the first group of patients, in which only one 10 minute sample was withdrawn, the plasma volume was calculated by using the following formula:

$$\text{Plasma volume} = \frac{\text{Activity of standard} \times \text{volume injected} \times \text{dilution of standard}}{\text{Activity of sample}}$$

The total blood volume was then estimated by using the average corrected hematocrit:

$$\text{Total blood volume} = \frac{\text{Plasma volume}}{1 - \text{corrected hematocrit}}$$

In the second group of patients, in which 3 accurately timed samples were withdrawn, each sample was counted just as with the 1 sample technique. From these 3 samples the disappearance curve of the material from the blood stream was obtained. By using the slope of the disappearance curve the activity at the time of injection was calculated. By using the activity at time zero the plasma and total blood volumes were estimated as with the first group of patients.

Results. The mean plasma volume in the first group of patients, by a 1 sample withdrawal, was found to be 48.9 milliliters per kilogram of body weight with a standard deviation of 5.09 (Table I). In the second group of patients, in which 3 accurately timed samples were withdrawn, the mean plasma volume was found to be 43.3 milliliters per kilogram of body weight, with a standard deviation of 5.97.

The mean total blood volume in the first group of subjects was found to be 82.3 milliliters per kilogram with a standard deviation of 7.4. The second group showed a mean total blood volume of 77.7 milliliters per kilogram with a standard deviation of 9.48.

The results of all cases of the first group fell within 3 standard deviations of the mean, whereas all cases of the second group fell within 2 standard deviations of the mean.

The difference between the two arithmetic means of the plasma volumes as done in groups I and II was more than 3 standard errors of the difference between the two means. Since the actual difference was 5.6 and the standard error of the difference between the two means was 1.75, the difference is statistically significant and is unlikely to have been due to chance.

The difference between the two arithmetic means of the total blood volumes of groups I and II was less than 3 standard errors of the difference between the two means. The actual difference was 4.6 and the standard error of the difference between the means was 2.69.

Discussion. When the 3 sample technique was used the values for the plasma volume are lower than the ones obtained by the 1 sample technique. The 3 sample technique gave the more consistent, and probably the more accurate, results. Extrapolation of the disappearance slope to the time of injection accounts for the loss of the material from the blood stream, the loss due to diffusion of the material into the lymph, and the variations in the initial mixing rate.

The statistical significance of the difference between the two means for the total blood volumes is questionable; however, it is our opinion that the difference is significant and that the hematocrit is the predominant source of error.

Summary. Two methods of determining plasma volume utilizing iodinated human serum albumin have been compared. Lower and more consistent values were obtained in normal adult patients by use of the 3 sample technique, when 3 accurately timed samples are withdrawn and the activity at time of injection is calculated by using the slope of the disappearance curve. In the estimation of the total blood volume the hematocrit, even

TABLE I.—PLASMA AND TOTAL BLOOD VOLUME DETERMINATIONS WITH IODINATED HUMAN SERUM ALBUMIN

Group I—One Sample Technique

Case No.	Age, yrs.	Ht., in.	Weight kgm.	Hematocrit	Corrected hematocrit	Plasma volume, ml.	Ml./kgm.	Total blood vol., ml.	Ml./kgm.
1	30	71	89.5	.476	.457	3464	38.7	6379	71.3
2	30	69	58.6	.490	.470	2966	50.6	5596	95.5
3	28	72	81.4	.486	.467	3884	47.7	7287	89.5
4	22	68	63.6	.430	.413	2933	46.1	4996	78.6
5	40	66	63.6	.440	.422	2857	44.9	4943	77.7
6	26	76	84.1	.410	.394	4704	55.9	7762	92.3
7	64	66	74.1	.440	.422	3121	42.1	5399	72.9
8	66	70	56.8	.420	.403	2855	50.3	4782	84.2
9*	22	63	52.3	.410	.394	2393	45.8	3949	75.5
10	37	72	64.5	.410	.394	3260	50.5	5379	83.4
11*	27	68	61.4	.370	.355	3052	49.7	4732	77.1
12*	22	66	58.6	.355	.341	2934	50.1	4452	76.0
13*	24	62	52.3	.460	.442	2466	47.2	4427	84.6
14*	25	65	52.7	.384	.369	3286	62.4	5208	98.8
15	21	70	78.2	.440	.422	3735	47.8	6462	82.6
16	22	65	68.2	.380	.365	3217	47.2	5066	74.3
17	24	68	81.8	.430	.413	3804	46.5	6480	79.2
18	41	68	64.5	.470	.451	3144	48.7	5727	88.8
19	25	68	76.8	.330	.317	4442	57.8	6504	84.7
20	67	70	68.6	.410	.394	3303	48.1	5450	79.4
Mean							48.9		82.3
Standard deviation							5.09		7.4
Coefficient of variation, per cent							10.4		8.99

Group II—Three Sample Technique

Case No.	Age, yrs.	Ht., in.	Weight kgm.	Hematocrit	Corrected hematocrit	Plasma volume, ml.	Ml./kgm.	Total blood vol., ml.	Ml./kgm.
1	24	69	77.3	.465	.446	2954	38.2	5332	70.0
2	21	73	84.5	.475	.456	3555	42.1	6535	77.3
3	77	66	50.4	.465	.446	2326	46.2	4199	83.8
4	43	71	73.2	.456	.438	3206	43.8	5705	77.9
5	20	69	56.8	.454	.436	2222	39.1	3940	69.4
6	24	70	78.3	.520	.499	2847	36.4	5683	72.6
7	22	68	60.9	.440	.422	2613	42.9	4521	74.2
8	22	71	67.3	.480	.461	2777	41.3	5152	76.6
9*	31	66	53.6	.420	.403	2828	52.8	4737	88.4
10	21	75	77.3	.500	.480	3888	50.3	7477	96.7
11	20	70	61.4	.500	.480	3141	51.2	6040	98.4
12*	28	65	53.2	.440	.422	2540	47.7	4394	82.6
13	51	72	90.5	.410	.394	4172	46.1	6884	76.1
14	35	72	95.5	.360	.346	4254	44.6	6505	68.2
15	20	76	81.8	.468	.449	3037	37.1	5482	67.0
16	22	69	72.7	.492	.472	2904	39.9	5500	75.7
17	22	69	62.3	.513	.492	2341	37.6	4608	72.9
18	19	68	79.1	.495	.475	2541	32.1	4840	61.1
19	22	71	82.3	.480	.461	3322	40.4	6163	74.9
20	20	67	54.5	.395	.379	3050	56.0	4911	90.1
Mean							43.3		77.7
Standard deviation							5.97		9.48
Coefficient of variation, per cent							13.8		12.2

*Female

though corrected, apparently still introduces a sizable error.

PART II: SERIAL DETERMINATIONS OF THE PLASMA VOLUME TO DETERMINE THE REPRODUCIBILITY OF RESULTS

Many investigators have used iodinated human serum albumin and Evans' blue dye to measure plasma volume. In surveying the literature there have been no reports of serial determinations of the plasma volume on the same patient by using iodinated human serum albumin, and only one report on 3 patients made with Evans' blue (5).

The purpose of this project was to determine and compare the reproducibility of plasma volume determinations using iodinated human serum albumin and Evans' blue dye in normal humans.

Selection of patients. Subjects were patients admitted for elective surgery to the surgical wards of the United States Naval Hospital, Bethesda, Maryland. Seven patients were studied with serum albumin and 12 with Evans' blue.

Methods. One group of patients was given serum albumin intravenously in doses of approximately 50 microcuries of radioiodine. From the opposite arm 3 accurately timed blood samples were withdrawn. Immediately following the withdrawal of the third specimen approximately 70 microcuries of iodinated human serum albumin were injected into the arm previously used for injection, and 3 ac-

curately timed specimens withdrawn from the arm, previously used for withdrawal. All specimens were withdrawn by syringes moistened with heparin and were placed into heparinized tubes.

The calculations of the plasma volume were made by the procedures described in part I, comparing results based on the first dose and then the second dose.

The second group of patients received Evans' blue dye, the dose depending on the weight of the individual, and 3 samples of blood were withdrawn from the opposite arm at the same time intervals as in the first group. A blood sample to be used as a blank was then withdrawn. Immediately thereafter, a second dose was administered and 3 samples of blood were again withdrawn at the designated time intervals. By using the method described by Chinard (2,3), the optical density of each specimen was determined and by means of the slope of the disappearance curve the density at the time of injection was estimated. From this value and the optical density of the standard the plasma volume could be calculated. The plasma volume was estimated on the basis of the first and then the second dose.

Results. With each group of patients, two values for the plasma volume were obtained. From these the mean, the standard deviation, and the coefficient of variation were calculated. The coefficient of variation, only, was utilized in each group to evaluate the reproducibility of each method of plasma volume determination.

In the series using the iodinated human serum albumin the coefficient of variation ranged from 0.67 to 7.30 per cent in the 7 cases with a mean of 3.38 per cent (Table II). All values fell within 2 standard deviations of the mean.

In the series using the Evans blue the coefficient of variation ranged in the 12 cases from 0.08 to 10.21 per cent with a mean of 3.54 per cent (Table II). All values fell within 3 standard deviations of the mean.

In Cases 7 and 8 the study was performed twice.

Discussion. The values obtained from the serum albumin series of cases represented a close degree of reproducibility, probably because of the slow disappearance of the material from the blood stream and the accuracy of the instruments used for counting.

The results obtained by using Evans' blue also show a good degree of reproducibility but a wider variation.

Inconsistent technical difficulties which may contribute to errors of the test are errors of volumetric measurement, injection technique, sampling technique, statistical errors of counting, adsorption of the material onto the walls of the syringe used for injection and most of all, human error.

These same errors carry over into the use of Evans' blue to determine the plasma volume. It has been found that in high dilutions of the dye there is a small change in the optical density for a large change of dilution. If insufficient dye is injected, the sensitivity of the determination is lessened because the dilution is great. This decrease in sensitivity further adds to the errors in the determination.

Summary. The reproducibility of results obtained by using Evans' blue and that by iodinated human serum albumin have been compared. The values for the plasma volume obtained by each method of determination show a good degree of reproducibility in the same patient.

PART III: COMPARISON OF THE PLASMA AND TOTAL BLOOD VOLUMES AS DETERMINED BY VARIOUS TECHNIQUES

During the last 20 to 25 years many studies have been made comparing the various methods of measuring blood volume. No reports are available comparing simultaneously in the same patient the blood volumes as measured by P^{32} tagged red blood cells, iodinated (I^{131}) human serum albumin, and Evans' blue dye. This study was undertaken as a preliminary portion of a project to evaluate plasma space expanders, both to standardize the tests and to choose the test which would give the greater degree of dependability.

Selection of patients. Subjects were patients admitted to the hospital for minor elective operations and corpsmen volunteers attached to the National Naval Medical Center, Bethesda, Maryland.

Methods. The use of radioactive phosphorus in tagging the red blood cells required more elaborate techniques than the method using Evans' blue dye or the serum albumin. The latter techniques have been described previously in parts I and II. The P^{32} tagged cell procedure required that a sample of blood be withdrawn and placed in a heparinized sterile tube with 100 microcuries of radiophosphorus. This tube was incubated 75 minutes at body temperature with frequent gentle agitations. The tube was then centrifuged, the plasma separated and discarded. The cells were then washed 3 times with the cold saline and following the final wash, reconstituted to approximately the original volume. Five milliliters of this final mixture of tagged cells and cold saline were used for injection.

The comparative study utilizing all 3 methods in the same patient was carried out as follows. The subject received intravenously first the dye and then the P^{32} tagged red blood cells. Three accurately timed samples of blood were withdrawn from the other arm. Immediately thereafter the iodinated human serum albumin was administered and 3 accurately timed samples of blood withdrawn. The final 3 samples were kept cold and the plasma separated immediately from the red cells.

The plasma volume was determined directly with Evans' blue by Chinard's method (2,3) and by using iodinated serum albumin as described in part I, in both instances utilizing the 3 sample technique.

The first 3 specimens were used to determine the plasma volume by the Evans' blue method and the red cell mass by the P^{32} tagged red cell method. Each specimen for the P^{32} method was centrifuged, the plasma withdrawn and used for the Evans blue determination. The remaining cells were washed 3 times with cold saline and following the final wash were reconstituted to approximately the final volume. On each specimen a hematocrit was performed, and samples were prepared for counting by placing 3 milliliters of the mixture in a 25 milliliter volumetric flask and diluting with water to 25 milliliters. After each flask had been thoroughly mixed the contents were poured into a small Petri dish for counting. This furnished a sample of infinite thickness which was counted beneath a horizontally placed thin wall dipping tube in a horizontal lead shield, maintaining constant geometry. From the rate of disappearance of the activity from the blood stream the activity at time zero was calculated.

TABLE II.—SERIAL DETERMINATIONS OF THE PLASMA VOLUME TO ASCERTAIN THE REPRODUCIBILITY OF RESULTS

Using Evans' Blue

Case No.	Age, yrs.	Plasma volume on basis of first dose, ml.	Plasma volume on basis of second dose, ml.	Coefficient of variation, per cent
1	55	2594	2683	1.72
2	32	2475	2779	5.78
3	20	2279	2511	4.84
4	22	2806	2786	0.35
5	25	3110	3115	0.08
6	30	2902	3146	4.03
7	23	3696	4203	6.41
7	23	3865	3743	1.60
8	60	3942	3692	3.27
8	60	3290	3349	0.88
9	23	3203	3621	6.12
10	21	2792	3021	3.94
11	20	3302	3283	0.28
12	21	4095	3336	10.21
Mean coefficient of variation, per cent				3.54

Using Iodinated Human Serum Albumin

1	21	3441	3488	0.67
2	17	2755	2810	0.98
3	17	2003	2251	5.82
4	36	2377	2752	7.30
5	24	2954	3170	3.52
6	23	3129	3403	4.19
7	46	2840	2907	1.16
Mean coefficient of variation, per cent				3.38

By utilizing the activity of the standard, equivalent to the mixture prepared for injection, and the activity at time zero, the red cell mass could be estimated as follows:

$$\text{Red cell mass} = \frac{\text{Activity of standard} \times \text{volume injected}}{\text{Activity of specimen}}$$

The total blood volume was then estimated by the formula:

TABLE III.—COMPARISON OF THE PLASMA AND TOTAL BLOOD VOLUME AS DETERMINED BY RADIOACTIVE PHOSPHORUS TAGGED RED BLOOD CELLS, IODINATED HUMAN SERUM ALBUMIN, AND EVANS' BLUE

Case No.	Age, yrs.	Ht., in.	Wt., kgm.	Hematocrit	Corr. hemat.	Radioactive phosphorus tagged cells						Iodinated human serum albumin				Evans' blue				Total body hematocrit*	Ratio of TBH to peripheral hematocrit
						Red cell mass	Ml./kgm.	Plasma volume	Ml./kgm.	Total blood volume	Ml./kgm.	Plasma volume	Ml./kgm.	Total blood volume	Ml./kgm.	Plasma volume	Ml./kgm.	Total blood volume	Ml./kgm.		
1	22	70	72.7	.466	.447	2818	38.7	3486	48.0	6304	86.7	3904	53.7	7060	97.1	3765	51.8	6808	93.6	.419	.937
2	21	71	78.2	.435	.418	2490	31.9	3467	44.3	5957	76.2	3813	48.8	6552	83.8	4024	51.5	6914	88.4	.395	.945
3	22	71	65.9	.430	.413	1942	29.5	2760	41.9	4702	71.4	3326	50.5	5666	86.0	2875	43.6	4898	74.3	.369	.893
4	41	67	84.1	.457	.439	1958	23.2	2502	29.8	4460	53.0	3053	36.3	5442	64.7	4300	51.1	7665	91.1	.391	.891
5	19	68	68.2	.480	.461	2862	41.9	3346	49.1	6203	91.0	3504	51.4	6501	95.3	3676	53.9	6820	100.0	.450	.976
6	31	70	65.7	.438	.420	1817	27.6	2509	38.2	4326	65.8	3321	50.4	5710	86.9	3564	54.2	6145	93.5	.354	.843
7	43	71	97.7	.475	.456	2715	27.7	3239	33.2	5954	60.9	3932	40.2	7228	74.0	3941	40.3	7244	74.1	.408	.895
8	20	65	57.7	.500	.480	2541	44.1	2753	47.7	5294	91.8	2873	49.8	5525	95.8	2677	46.4	5148	89.2	.469	.977
9	42	71	61.8	.420	.403	1743	28.2	2582	41.8	4325	70.0	3063	49.6	5131	83.0	3135	50.7	5251	85.0	.362	.901
10	20	75	95.9	.465	.446	2437	25.4	3027	31.6	5464	57.0	4070	42.4	7347	76.6	3887	40.5	7016	73.2	.375	.841
11	20	70	57.6	.490	.470	1725	29.9	1945	33.8	3670	63.7	2219	38.5	4187	72.7	2950	51.2	5566	96.6	.437	.930
12	20	67	62.7	.450	.432	1851	29.5	2434	38.8	4285	68.3	2514	40.1	4426	70.6	2600	41.5	4577	73.0	.424	.981
13	22	65	72.7	.470	.451	2136	29.4	2538	34.9	4674	64.3	2695	37.1	4909	67.5	2818	38.8	5133	70.6	.442	.980
14	37	72	85.5	.460	.442	1863	21.8	2352	27.5	4215	49.3	2784	32.6	4989	58.4	3342	39.1	5989	70.0	.401	.907
15	23	70	75.3	.433	.416	2642	35.0	3709	49.3	6351	84.3	3810	50.6	6524	86.6	3546	47.1	6072	80.6	.409	.983
16	20	74	88.6	.473	.454	2362	26.6	2841	32.1	5203	58.7	4114	46.4	7675	86.6	4443	50.1	8137	91.8	.365	.804
17	28	72	88.6	.450	.432	2559	28.9	3365	38.0	5924	66.9	3616	40.8	6366	71.9	2864	32.3	5042	56.9	.414	.958
18	22	71	68.2	.441	.423	1774	26.0	2420	35.5	4194	61.5	3124	45.8	5414	79.4	2835	41.6	4913	72.0	.362	.856
19	21	65	60.0	.456	.438	2075	33.6	2662	45.3	4737	78.9	2640	44.0	4689	78.2	2727	45.5	4852	80.9	.440	1.005
20	21	66	72.7	.420	.403	1528	21.1	2264	31.1	3792	52.2	2762	38.0	4626	63.6	2957	40.7	4953	68.1	.356	.883
21	26	71	75.0	.454	.436	1871	25.0	2422	32.3	4294	57.3	2996	39.9	5312	70.8	3122	41.6	5535	73.8	.384	.881
22	65	65	67.3	.450	.432	2252	33.6	2961	43.9	5213	77.5	2673	39.7	4706	69.9	5271	44.5	5271	78.3	.457	1.058
23	22	72	87.2	.488	.468	2282	26.2	2594	29.7	4876	55.9	3955	45.3	7297	83.6	4238	48.6	7966	91.4	.366	.782
24	32	67	64.5	.474	.455	2033	31.6	2435	37.7	4468	69.3	2232	34.6	4095	63.5	2861	44.4	5250	81.4	.477	1.048
25	33	71	66.4	.505	.485	2448	36.9	2599	39.1	5047	76.0	2922	44.0	5674	85.5	2891	43.5	5614	84.5	.456	.940
Mean							30.1		38.2		68.3		43.6		78.1		45.4		81.3		.924
Standard deviation							5.74		6.52		11.8		5.79		10.5		5.43		10.4		
Coefficient of variation, per cent							19.1		17.1		17.3		13.3		13.5		11.9		12.8		

*Using P^{32} determined red cell mass and IHSA determined plasma volume.

$$\text{Total blood volume} = \frac{\text{Red cell mass}}{\text{Corrected hematocrit}^1}$$

Results. The total blood volume values obtained with radioactive phosphorus tagged red blood cells were lower than similar volumes obtained by the other two methods (Table III). The mean red cell mass was 30.1 milliliters per kilogram with a standard deviation of 5.74, all values of the red cell mass falling within 3 standard deviations of the mean. The mean plasma volume by the method was 38.2 milliliters per kilogram with a standard deviation of 6.52, all values falling within 2 standard deviations of the mean; the mean total blood volume was 68.3 milliliters per kilogram with a standard deviation of 11.8. All values of the total blood volume were seen to fall within 3 standard deviations of the mean.

[1]See part I.

By using the iodinated human serum albumin method values were obtained that were between the levels obtained from the other two methods. The mean plasma volume was 43.6 milliliters per kilogram with a standard deviation of 5.79, all values falling within 2 standard deviations of the mean. The mean total blood volume was 78.1 milliliters per kilogram with a standard deviation of 10.5, all values falling within 2 standard deviations of the mean.

The Evans blue technique produced the highest values for plasma volume and total blood volume determinations. The mean plasma volume was 45.4 milliliters per kilogram with a standard deviation of 5.43, all values falling within 3 standard deviations of the mean. The mean total blood volume was 81.3 milliliters per kilogram with a standard deviation of 10.4, all values falling within 2 standard deviations of the mean

By using the values for the red cell mass determined with P^{32} tagged red blood cells and the values for the plasma volume determined with iodinated human serum albumin the total body hematocrits were calculated. From these data the ratios of the total body hematocrit to the peripheral vessel hematocrit were determined. These ratios ranged from a low of 0.782 to a high of 1.058 with the averages being 0.924.

Discussion. Probably the most accurate of estimations is a combination of methods, namely the radiophosphorus tagged red cell method for the red cell mass and the iodinated human serum albumin or Evans' blue method for the plasma volume. By a combination of methods each value is measured directly and is not dependent upon the hematocrit.

The ratio between the total body hematocrit and the peripheral vessel hematocrit herein determined is in agreement with that determined by other investigators. Root and associates, using the factor 0.96 to correct their hematocrits for plasma trapped among packed cells, found in the 14 human experiments and in 26 of the 29 animal experiments the ratio of the total body hematocrit to the peripheral vessel hematocrit to range from 0.90 to 1.08. They stated that their results do not disprove that the cell to plasma ratio is less in the capillaries than in the large vessels, but only indicated that the amount of blood present in the small vessels was not large enough for the unequal distribution of red cells in these vessels to affect greatly the estimation of the blood volume as calculated from the dye and hematocrit reading under these conditions.

Meneely and associates compared the results obtained by Fe^{59} tagged red cells and Evans' blue dye and found the peripheral venous hematocrit to be higher than the total body hematocrit. When their results were recalculated by using the correction factor 0.96 for the hematocrit, the ratio between the total body hematocrit and the peripheral vessel hematocrit was found to average 0.923.

Berson and Yalow, using the plasma volume as determined with serum albumin and the red cell volume as determined with P^{32} tagged red cells, found the mean value for the ratio of the average body hematocrit to the peripheral vessel hematocrit to be 0.924 with a range from 0.860 to 0.996, by using a correction factor of 0.98 for the hematocrits. When a correction factor of 0.96 for the hematocrit was used the mean value for the ratio of the average body hematocrit to the peripheral vessel hematocrit was found to be 0.943 with a range from 0.875 to 1.024.

Summary. The plasma and total blood volume values obtained by using radioactive phosphorus tagged red blood cells, iodinated human serum albumin, and Evans' blue have been compared simultaneously in the same patient. The radiophosphorus tagged red cell method gives the lowest values, the iodinated human serum albumin method the middle ones, and the Evans blue the highest. Probably the most accurate determination of total blood volume involves a combination of tests in which the red cell mass and plasma volume are measured directly, and it does not depend on the hematocrit determination.

CONCLUSIONS

From the studies herein described many valid and important conclusions may be drawn.

In part I it was demonstrated by using iodinated human serum albumin that the 3 sample withdrawal method gives the more

consistent results. Making use of the disappearance curve accounts for the loss of the material from the blood stream, the loss due to diffusion of the material into the lymph, and the variations in the initial mixing rate.

In part II the values for the plasma volume obtained by utilizing Evans' blue or iodinated human serum albumin show a good degree of reproducibility in the same patient in spite of a number of technical difficulties of the test.

In part III the plasma and total blood volumes obtained by using radioactive phosphorus tagged red blood cells, iodinated human serum albumin, and Evans' blue were compared simultaneously in the same patient. The first test gives the lowest values, the second the middle values, and the third the highest. By using the above data it was demonstrated that the total body hematocrit is lower than the peripheral vessel hematocrit. On the basis of theoretical considerations we believe it is better to determine the total blood volume by adding the red cell mass determined by radiophosphorus tagged red blood cells and the plasma volume obtained with iodinated human serum albumin. Both are direct measurements and do not introduce the error of the peripheral vessel hematocrit.

This work on blood volumes is in a continuing state, and at present studies are underway or contemplated to compare the present studies with the chromium^{51} determination of the red cell mass.

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A BEDSIDE MANOMETRIC TEST TO LOCALIZE BALLOON OF A MILLER-ABBOTT TUBE IN INTESTINAL OBSTRUCTION

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DECOMPRESSION of the intestinal tract by means of a Miller-Abbott tube is a valuable procedure, though it should be realized that the tube is potentially a two-edged sword which can either defend or defeat the patient, depending upon its use. Its chief use lies in the treatment of paralytic ileus and in the preoperative and postoperative decompression of cases of mechanical obstruction. Its danger lies in the temptation to defer operation unduly in cases of obstruction where there may be strangulation, and this includes many cases. Gangrene or perforation of the bowel may occur while operation is delayed by the attempts to pass a tube.

The chief problem in the use of the tube consists in getting it past the pylorus. The balloon must be emptied of air in order to pass the pyloric sphincter, but must be inflated with air after it has passed the pylorus so that it will advance down the intestine as rapidly as possible. Hence, it is essential to know when the balloon has passed the pyloric sphincter so that air may be injected into it. The fluoroscope or portable x-ray machine can usually determine the anatomic site of the tube, but the disadvantages of this established method are several, viz.: moving the ill patient, obtaining the services of the radiology staff at odd hours, possible necessity of repeated examinations, and an added consideration is the expense to the patient. Various bedside tests to determine when the balloon has passed the pylorus have been described, but, to my knowledge, none is completely objective or entirely reliable.

The purpose of this paper is to describe a simple, objective test which has been developed and applied in 56 cases of intestinal intubation. The test is based on the fact that the inflated balloon cannot expand as freely in the duodenum as it can in the stomach.

If the balloon is inflated to a given diameter, it will expand quite freely if it lies in the stomach. If, however, the balloon lies in the duodenum and the same amount of air is injected into it, expansion of the balloon will be restricted by the duodenum, and the pressure in the balloon will therefore rise. In this series of cases it has been found that for any given patient, with the balloon in the duodenum and inflated to a diameter of 2 inches, the pressure is at least twice as great as when the balloon lies in the stomach.

During the first part of the series, the balloon was inflated to a diameter of 1½ inches, and the pressure recorded by a water manometer. Some of the results were rather indecisive (Table IA) and in the remaining cases the balloon was inflated to a diameter of 2 inches and a mercury sphygmomanometer used. This change in technique gave duodenal pressures that were consistently double the gastric pressures (Table IB). This is shown graphically in Figure 2 which illustrates the pressures of the cases listed in Table IB. In Figure 2 the vertical scale (duodenal pressure) is twice the horizontal scale (gastric pressure). Therefore, if the duodenal pressures are twice as high as the gastric pressures, the dots marking the pressure readings should lie above the diagonal straight line. With several very minor exceptions they do.

Before inserting the tube, the amount of air required to inflate the balloon to a 2 inch diameter is determined. The tube is then inserted into the stomach in the usual manner, and 2 cubic centimeters of mercury are injected into the balloon. With the balloon in the body of the stomach, it is inflated to a 2 inch diameter, and the pressure is recorded

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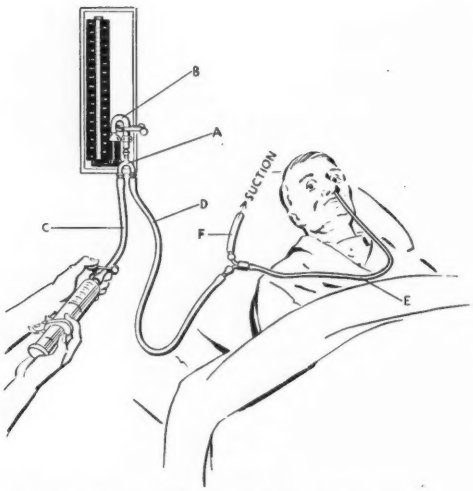

Fig. 1. Apparatus used for intestinal intubation.

by the sphygmomanometer. Then an attempt is made to pass the deflated balloon through the pylorus and whether or not it has actually gone through is determined by reinflating the balloon to a 2 inch diameter and measuring the pressure. If the pressure is at least twice as great as that obtained in the stomach, the balloon has passed the sphincter. If it is less than twice as great, it has not. If unsuccessful in one position of the patient, others are tried.

STEP BY STEP PROCEDURE

To be of greatest practical value, not only the method of applying the test but also the precise method of passing the tube is described. Interns, unfamiliar with intestinal intubation, have found the following instructions sufficient for successful intubation.

Apparatus. Have a tray prepared containing the following: Miller-Abbott tube, two 50 cubic centimeter syringes with adapters, mercury, one 2 cubic centimeter syringe, cleansing tissue, half inch adhesive tape, surgical lubricant jelly, cup of drinking water, kidney basin, ruler, and 2 towels.

Detach a mercury sphygmomanometer from its arm cuff and connect it to a Y-connector (*A*, Fig. 1), by its tube, *B*. To each of the other 2 arms of the Y, join a piece of rubber tubing (*C* and *D*). In one of these (*C*), insert an adapter for a 50 cubic centimeter syringe, so that a syringe can be connected and disconnected easily. Connect the tube (*D*) on the other arm of the Y to the balloon side of the Miller-Abbott tube. Apply a spring clamp to the syringe tube (*C*), close to the adapter, and another spring clamp to the tube (*B*), joining the sphygmomanometer to the Y-piece. These clamps are best if of such a design that they clamp off the tube continuously unless held open.

Technique. If the patient is a female ask her to void before commencing to avoid the possibility of having to move her into a convenient position for this during the procedure.

It is most convenient to work from the patient's right side.

Mark one of the 50 cubic centimeter syringes with a piece of adhesive. This syringe is kept dry for inflating the balloon while the other is used for aspirating gastric contents. If water is injected into the small bore tube leading to the balloon, it interferes with the ready transmission of pressure readings.

Before inserting the tube, inject air through the suction side to ensure that it is patent. Next, determine the amount of air necessary to inflate the balloon to a diameter of 2 inches by holding it above a ruler and inflating. A new Miller-Abbott tube usually requires 80 cubic centimeters of air. Hold the inflated balloon under water to ensure that it does not leak. If the tube is not new, one occasionally finds that the balloon has been previously tied on so tightly that air cannot readily be drawn back and forth from it. Such a tube cannot be used easily. Next, deflate the balloon and lubricate the terminal 2 feet of the tube with ordinary surgical lubricant jelly. Pontocaine spray is to be avoided if possible because of: (a) possible allergic reactions, and (b) possible violent coughing from aspirating the sips of water given with the tube.

The procedure is continued as follows:

1. With the patient either lying or propped up in bed (the latter position is better for the initial swallowing of the tube), lift up the tip of the nose and pass the tube along the floor of the nasopharynx. When it reaches the oropharynx, give the patient sips of water to aid swallowing of the tube. Each time the

larynx rises in swallowing advance the tube. It is thus passed to the 60 centimeter mark.

2. Aspirate the stomach with the "wet" syringe. If the bed has been raised to facilitate swallowing of the tube, lower it to the horizontal position. Inflate the balloon with about 50 cubic centimeters of air; withdraw the tube until a tug is felt. The balloon is now engaged at the cardiac end of stomach.

3. Holding the tube out from the nares, snugly but not tightly place an adhesive marker on the tube 9 inches from the nostril using a ruler. This is usually near the 75 centimeter mark.

4. Place the patient on his right side so that his back is exactly at right angles to the surface of the bed (*position 1*). His lower (right) arm is flexed in front of him, and his face just projects beyond the edge of the pillow to facilitate giving sips of water.

5. Aspirate the air from the balloon and inject 2 cubic centimeters of mercury into it. Lift up the tubing, loop by loop, to let the mercury drain into the balloon. Then forcibly inject 25 cubic centimeters of air to push the mercury in. There will be a sudden release of pressure on the syringe as the mercury goes into the balloon. Aspirate the air so that the balloon now contains only 2 cubic centimeters of mercury. The mercury is not readily aspirated back into the tube. Connect the balloon to the sphygmomanometer as described.

6. With small sips of water, and still on his right side, the patient swallows approximately 4 inches of tubing. The balloon will now lie in the body of the stomach.

7. Inject into the balloon the amount of air previously found necessary to inflate it to a diameter of 2 inches. Determine the pressure in the balloon by holding open the clamp leading to the manometer. This pressure is usually between 5 and 20 millimeters of mercury. Aspirate the air from the balloon.

8. With small sips of water, and with the patient still on his right side, advance the tube to the adhesive marker, i.e., to 9 inches beyond the cardiac orifice. The mercury-weighted balloon has then travelled along the lesser curvature and now lies either in the pyloric antrum with sufficient slack to permit it to pass the pylorus, or, if one is fortunate,

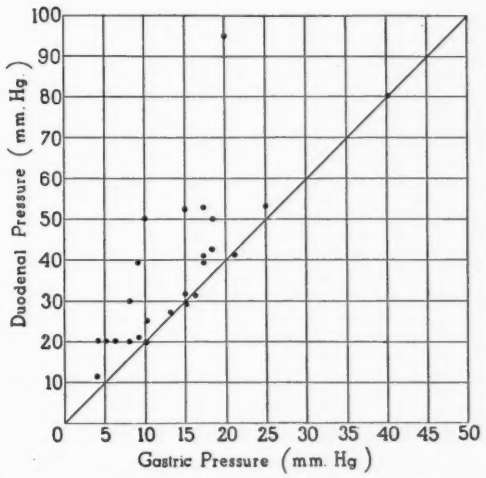

Fig. 2. Graph showing duodenal and gastric pressures of cases listed in Table IB.

it has already passed the pyloric sphincter. To determine if the balloon has passed the pylorus, again inflate it to a 2 inch diameter, and take a pressure reading. If the pressure reading is twice as high as the reading obtained with the balloon in the stomach, and is sustained, the balloon has passed the pylorus. Peristaltic contractions in the pyloric antrum will produce a rise in pressure, occasionally up to twice the level in the stomach, but the rise is not sustained, and when the peristaltic wave has passed off, the pressure drops to the same level as in the stomach. The demonstration of presence or absence of peristalsis is also of some clinical value in cases of paralytic ileus. There are also minor fluctuations of pressure of several millimeters of mercury due to respiration.

9. If the balloon has not passed the pylorus, again aspirate the stomach contents through the suction lumen and make one more attempt in this position, by emptying the balloon of air, pulling it up 4 or 5 inches, and having the patient swallow it again. If it is still not in the pylorus, one must repeat the procedure in other positions. These positions are, in order of preference:

Position 2. Lift up the patient's shoulders enough to allow his right arm to be extended and brought beneath his body and lie extended

TABLE IA.—BALLOON INFLATED TO 1½ INCHES DIAMETER AND PRESSURE MEASURED BY WATER MANOMETER

Case No.	Diagnosis	Degree of distention —maximum, 4+	Pressure in balloon in stomach, in. of water	Pressure in balloon in duodenum, in. of water	Entry of tube into duodenum proved	Time required to pass pylorus	Successful position
1	Small bowel obstruction	3+	7 –8	16 –18	progressed down	5 minutes	1
2	Small bowel obstruction	2+	7 –8	14 –20	x-ray	not known	1
3	Ruptured appendix	2+	7	20	x-ray	overnight	1
4	Postgastrectomy	2+	4	8 –16	x-ray	2 hours	7
5	Not known	4+	2 –4	7 – 8	progressed down	not known	2
6	Feeding tube	0+	3 –4	7 – 8	progressed down	not known	?
7	Small bowel obstruction	2+	7 –8	16 –20	progressed down	immediate	2
8	Small bowel obstruction	2+	5 –6	12 –14	progressed down	not known	?
9	Small bowel obstruction	1+	3 –4	12	x-ray	30 minutes	2
10	Carcinoma sigmoid	3+	2	8 – 9	x-ray	30 minutes	?
11	Subphrenic abscess	0+	6 –8	20	at operation	immediately	6
12	Preop. bowel resection	0+	4 –6	12 –16	at operation	immediately	2
13	Postop. bowel resection	1+	6 –8	12 –16	progressed down	overnight	2
14	Small bowel obstruction	1+	4 –5	7 – 9	progressed down	not known	?
15	Small bowel obstruction	2+	4 –5	12 –14	progressed down	not known	?
16	Postoperative ileus	3+	3½–4	5½– 6½	progressed down	not known	?
17	Small bowel obstruction	1+	4½	7 – 9	x-ray	immediately	1
18	Small bowel obstruction	1+	2 –3	5½– 9	progressed down	30 minutes	2
19	Postoperative ileus	1+	2	20	progressed down	1 hour	1
20	Postoperative ileus	2+	4 –5	10 –14	x-ray	immediately	4
21	Small bowel obstruction	1+	5 –6	16 –20	progressed down	2 hours	1
22	Peritonitis	2+	5 –6	8 –10	x-ray	2 hours	1
23	Large bowel obstruction	3+	5 –6	10 –20	progressed down	30 minutes	1
24	Small bowel obstruction	3+	4 –5	10 –13	x-ray	overnight	1
25	Strangulated hernia	2+	4 –6	8 –12	progressed down	immediately	6
26	Postoperative ileus	4+	6 –8	15 –16	progressed down	overnight	2
27	Large bowel obstruction	2+	6 –8	12 –16	progressed down	not known	2
28	Feeding tube	0+	3½–4	10 –12	progressed down	not known	?

behind him. Turn the patient toward his face, and support him with a pillow in front, so that he lies in a position midway between being on his abdomen and on his right side. His anterior body wall forms an angle of approximately 45 degrees with the surface of the bed.

Position 3. The patient is midway between being on his right side and on his back so that his back forms an angle of 45 degrees with the surface of the bed.

Positions 4, 5, and 6. These are the same as positions 1, 2, and 3 respectively but with the head of the bed cranked up to 45 degrees.

Position 7. The patient is sitting upright on the side of the bed.

In the majority of cases, positions 1 or 2 are successful. If they are not, and if the patient is co-operative and not too ill, the other positions may be tried.

In each position, withdraw and advance the empty balloon once or twice, then test it with a pressure reading to see if it has passed the pylorus. There is no advantage in withdrawing and advancing the tube more than twice in any position, for when it goes through the pylorus it does so readily. In one quarter of

TABLE IB.—BALLOON INFLATED TO 2 INCHES DIAMETER AND PRESSURE MEASURED BY A MERCURY SPHYGMOMANOMETER

Case No.	Diagnosis	Degree of distention —maximum, 4+	Pressure in balloon in stomach, mgm. of mercury	Pressure in balloon in duodenum, mgm. of mercury	Entry of tube into duodenum proved	Time required to pass pylorus	Successful position
29	Small bowel obstruction	1+	20	90–100	x-ray	4 hours	1
30	Small bowel obstruction	3+	10 –20	28– 30	x-ray	3 hours	3
31	Small bowel obstruction	2+	15	52	x-ray	not known	3
32	Small bowel obstruction	1+	18	50	progressed down	3 hours	1
33	Small bowel obstruction	2+	25	52– 55	x-ray	not known	?
34	Peritonitis	3+	20 –22	40– 42	x-ray	2½ days	1
35	Small bowel obstruction	2+	15	30– 32	progressed down	8 hours	1
36	Small bowel obstruction	2+	8	30	x-ray	5 hours	3
37	Small bowel obstruction	2+	16 –20	38– 46	x-ray	immediately	2
38	Small bowel obstruction	2+	16	30– 32	x-ray	immediately	1
39	Postgastrectomy	2+	8	20	x-ray	6 hours	7
40	Small bowel obstruction	2+	4 – 6	14– 26	progressed down	immediately	2
41	Paralytic ileus	2+	8	20	progressed down	immediately	2
42	Paralytic ileus	3+	16 –18	38– 40	progressed down	immediately	2
43	Small bowel obstruction	1+	8 –10	38– 40	x-ray	24 hours	1
44	Pelvic abscess	2+	4	20	progressed down	1 hour	1
45	Preoperative carcinoma sigmoid	0+	6	20	at operation	2 hours	1
46	Paralytic ileus	3+	10	50	progressed down	immediately	1
47	Feeding tube	0+	3½– 4	10– 12	progressed down	not known	?
48	Preoperative bowel resection	1+	15 –20	40	x-ray	2½ hours	7
49	Postoperative ileus	2+	16 –18	48– 55	progressed down	1 hour	3
50	Small bowel obstruction	2+	12 –14	24– 30	progressed down	1 hour	2
51	Paralytic ileus	2+	10	20	progressed down	immediately	1
52	Small bowel obstruction	2+	10	20– 30	progressed down	overnight	1
53	Postoperative ileus	3+	40	80	x-ray	overnight	5

Note: In Case 43, the tube could not be passed under the fluoroscope, but passed the pylorus after 24 hours in bed.
Case 53 was an infant 1 week old. An infant Miller-Abbott tube was used with ¾ cubic centimeters of mercury, and inflated to a diameter of 1¼ inches with 45 cubic centimeters of air (for pressure readings).

the cases, the balloon dropped into the pylorus immediately in one of these positions.

When inflating the balloon for a pressure reading, one sometimes notes that the tube emerges from the nostril 1 or 2 inches. This circumstance is due, as shown under the fluoroscope, to the inflated balloon being regurgitated slightly from the pyloric antrum and shows at least that the balloon is actually in the antrum. Occasionally, with the tube in the duodenum or pyloric ring, inflation causes some pain due to distention of the bowel. This condition has not been troublesome or severe and is accompanied by pressure rise indicating that the balloon is passing a tight sphincter.

TABLE IC.—CASES IN WHICH TUBE WOULD NOT GO THROUGH PYLORUS IN ANY POSITION

Case No.	Diagnosis	Degree of distention—maximum, 4+	Pressure inballoon in stomach, mgm. of mercury	No entry of tube into duodenum
54	Paralytic ileus	4	8–10	Tube could not be passed in 24 hours
55	Paralytic ileus	4	12–18	Tube could not be passed in 24 hours
56	Carcinoma stomach	3	6– 8	Tube could not be passed in 24 hours

During any of these maneuvers, when the pressure reading shows that the balloon is in the duodenum, inject 25 cubic centimeters of

air into the empty balloon, clamp off the balloon tip, and attach the suction tip to the suction apparatus. Tape the forceps on the balloon tip shut so that the balloon cannot be irrigated in error. Leave the patient in the position in which the tube passed through the pylorus until the tube has advanced an inch or 2, or up to half an hour. He may then lie flat on his back, and when the tube has advanced another inch or 2, he may lie in any position he wishes. Tape the tube to the face by a strip of tape placed obliquely above and lateral to the eye, so that the tube will not lie in front of his eye, and leave enough slack so that 3 or 4 inches of tube can pass into the nose. As this slack is taken up the nurse tapes up another loop. The suction side of the tube is irrigated every 2 hours with 10 cubic centimeters of water in a syringe. For the rare doubtful pressure test further aid is obtained by withdrawing the balloon (inflated to a diameter of 2 inches) to feel for a sharp tug at the pyloric ring, or by taking a roentgenogram.

If the balloon has not passed through the pylorus in any of the above positions, there are two alternatives: (1) Ask the roentgenologist to attempt to pass the tube under the fluoroscope. In 3 cases in this series the roentgenologist attempted to pass a tube where the maneuvers already mentioned were unsuccessful. In none of these could the tube be passed under the fluoroscope. (2) With the patient placed in position 1 and made absolutely as comfortable as possible by pillows, withdraw the tube to the cardia, advance it again to the mark 9 inches beyond the cardia, and tape it firmly to the nose at this point. This allows sufficient slack for the tube to pass through the pylorus but prevents the tube from being accidentally pulled out. Attach the suction apparatus to the suction lumen, check the balloon to be sure that it is empty of air, and leave the patient in this position for several hours or even overnight. A card can be left with the nurse with simple written instructions for her to inflate the balloon at half hour intervals and take a pressure reading. If the balloon has still not passed the pylorus, which is only in exceptional cases, repeat the procedure, using position 2. Such prolonged attempts, however, are usually justified only in cases of paralytic ileus in which operation is not contemplated, or in mechanical obstruction, when it is certain that no strangulation is present. In cases of suspected strangulation when the tube will not pass the pylorus and operation is indicated, one should not wait for the Miller-Abbott more than from 2 to 6 hours (as required for correction of fluid balance) but should operate with the decompression obtained by gastric suction only.

To find a simple and reliable means of relaxing the pyloric sphincter provides a worthy challenge for further research. The mechanism of action of this sphincter is not completely understood. It is the author's opinion that most cases of delay in passing the Miller-Abbott tube are due to persistent spasm of this powerful sphincter. Several procedures have been tried in this series in an effort to obtain relaxation but without any consistent success. These included lavage with warm water, lavage with ice water, hypodermic injection of 1/150 grain of atropine sulfate, injection of 200 to 500 cubic centimeters of air into the stomach, and on several occasions installation into the stomach of 50 to 100 cubic centimeters of 1 per cent novocain as described by Roka and Lajtha. None of these procedures appeared to be of any appreciable value, however, they were not used in a large number of cases and further study of this subject would be valuable.

SUMMARY

A simple test is described to determine when a Miller-Abbott tube has passed through the pylorus. It is based on the fact that the inflated balloon cannot expand as freely in the duodenum as it can in the stomach. The test depends on inflating the balloon so that it fills the duodenum, and measuring the pressure in the balloon with a sphygmomanometer. Its use in 56 cases of intestinal intubation is described.

The technique of intestinal intubation is described in detail.

REFERENCE

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POLYVINYLPYRROLIDONE IN SEVERE BURN SHOCK

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POLYVINYLPYRROLIDONE is a new and useful agent in the treatment of early burn shock, as first attested to in 1941 by Schulz and Orator. Subsequently others have described its effectiveness.

The hydrophilic character and osmotic activity of polyvinylpyrrolidone are factors which increase and maintain circulating blood volume. Furthermore, the ability of the PVP molecule to bind or adsorb toxins may give it additional value in combating burn toxicity. These reported experiences plus the additional consideration that PVP is inexpensive, completely sterilizable, producible in unlimited quantities, nonantigenic, and well tolerated by the patient assure polyvinylpyrrolidone an important role in burn therapy.

We describe here our experience, at the Harlem Hospital, New York City, with the use of PVP-macrose[1], in the treatment of 8 severely burned patients.

CLINICAL AND LABORATORY TESTS

A number of controlled observations were made in this group; i.e., serial blood pressures, pulse rates, hematocrits, whole blood and plasma specific gravities, and other vital signs relative to the clinical status of the patient. Liver function tests, including cephalin flocculations, van den Bergh, total serum protein and albumin-globulin ratio determinations, were carried out before, and at intervals after, infusion of this material. Serial blood volume determinations (Evans' blue method) following therapy and PVP urinary excretion rates were done on 4 patients.

RESULTS

Cases treated are summarized in Table I. Two representative cases are given in detail:

From the Departments of Surgery of Harlem Hospital, Department of Hospitals, and Columbia-Presbyterian Medical Center, New York.

[1]PVP-macrose, used in this study, is a 3.5 per cent polyvinylpyrrolidone in Ringer's solution.

CASE 4-B. C.W., Hospital No. 52-4836. Total burn area 60 per cent. The patient was brought to the hospital after her clothing had accidently caught fire and she had run into the street. There were extensive flame burns of the body and extremities. Previous history was not relevant.

Physical examination disclosed: a pulse rate of 150 per minute, thready in character; respirations were 34 per minute, irregular. The patient was a small, undernourished (15.6 kgm.), 6 year old colored female in acute distress, restless and apprehensive, complaining of pain and thirst. The area of burn (Fig. 1) extended from the lower face to the groin anteriorly, and from the occiput to the gluteal folds posteriorly. This entire area appeared to be third degree burn. The shoulders and upper extremities were also burned. The more proximal portions appeared to be third degree, and the more distal portions second degree burns. The lower extremities were not involved beyond the areas described.

The patient's burns were dressed with sterile vaseline gauze dressings. PVP was started by cutting down on an anterior tibial vein. The hematocrit fell from 45.8 to 30.7 per cent in the 2½ hours during which 1,500 cubic centimeters of PVP were administered. The urine, which was initially scanty and port wine in color, increased in volume and gradually cleared of hemoglobin in approximately 12 hours after the beginning of treatment. A second administration of PVP was given to this patient on the fifteenth hospital day and at that time a fall of the hematocrit was observed from 43.2 to 29.7 per cent 4 hours after the administration of 1,000 cubic centimeters of PVP was started. With the second infusion of PVP, the patient developed a questionable reaction consisting of an elevation of temperature to 104 degrees F. and a pulse rate of 140 per minute. There was no definite chill, dyspnea, cyanosis, or subjective feeling of discomfort. An infusion of 500 cubic centimeters of glucose in water was continued slowly, and the patient was given alcohol sponges, and oxygen by nasal catheter. Within 6 hours the temperature had returned to 99.8 degrees F., and the pulse rate to 122 per minute. The effect of increasing blood volume at this time with products of tissue necrosis may have been the cause of this reaction. The amounts of blood and plasma and the days on which they were given, in addition to the PVP administered, are indicated in Figure 2. The course of the patient in the hospital was complicated by severe and persisting infection of the burned areas in spite of several antibiotics and frequent redressings. The unavailability of sufficiently large areas of skin for grafting made plans for immediate

TABLE I.—SUMMARY OF BURN CASES

Case	Extent of burn	Amount of PVP given	Change in clinical status	Change in blood vol.	Change in hematocrit	Liver function studies	Outcome of case
1-B MS 31 yrs. Male 52-4639	20% burn—2% 1st° 15% 2nd° 3% 3rd°	2000 cc. in 2¼ hours	Immediate improvement in blood pressure and character of pulse. Decrease in toxicity	3739 to 4887 cc. in 24 hours	51.4 to 44.8% in 2 hours. Rise to 49.7% at 6 hours	Negative	Transferred to another hospital. Course uncomplicated. Improved
2-B SG 44 yrs. Male 52-4640	20% burn—3-4% 1st° 15% 2nd° 1-2% 3rd°	2000 cc. in 2 hours	Rise in blood pressure and slowing and improvement in character of the pulse		53.6 to 43.3% in 2 hours. Rise to 47.6% at 36 hours	Cephalin flocculation 2 plus on 2nd hospital day	Transferred to another hospital. Course uncomplicated. Improved
3-B AG 54 yrs. Female 52-1014	45% burn—1% 1st° 14% 2nd° 30% 3rd°	1500 cc. in 4 hrs. 1st day. 1500 cc. in 3½ hrs. 2nd day	Marked improvement in pulse character and toxicity. Urine output also improved. Similar improvement at time of second administration		53.3 to 48.3% in 4 hours. Rise to 58.3% at 20 hrs. with subsequent fall to 47.7% 10 hrs. after 2nd PVP	Alkaline phosphatase 11.7 Bodansky units on 5th day. Cephalin flocculation negative	Patient died on 11th hospital day of pneumonia and cardiac failure. Autopsy
4-B CW 6 yrs. Female 52-4836	60% burn—15% 2nd° 45% 3rd°	1500 cc. in 2¼ hrs. 1st day. 1000 c.c. in 4 hrs. on 15th day	Marked improvement in pulse, toxicity, and urinary output. Gross hemoglobinuria cleared in about 10 hrs. Improvement in toxicity after 2nd administration	1337 to 2066 cc. in 6½ hours	45.8 to 30.7% in 2½ hours. Rise to 50.4% in 24 hours Fall from 43.2 to 29.7% at time of 2nd administration (15th day). Rise to 34.5% in 24 hours	Cephalin flocculation 3 plus on 73rd hospital day. Negative previously	Patient died on 79th hospital day of pneumonia. Autopsy
5-B* MM 37 yrs. Female 52-5559	60% burn—5% 1st° 25% 2nd° 30% 3rd° Severe burn of oropharynx	1000 c.c. in 1 hr. 1st day. 2000 c.c. in 4 hrs. 5th day	Marked improvement in pt's stupor and toxicity. Improvement in pulse and output of urine which completely cleared of hemoglobin in 48 hrs.	5886 to 6038 c.c. in 48 hrs.	No data on admission. Fall from 55.5 to 46.1% in 4 hrs. (5th day). Rise to 54.4% in 48 hours	Negative	Patient died on 13th hosp. day of pneumonia following necrotizing tracheobronchitis. No autopsy.
6-B TG 4 yrs. Male 52-7431	30% burn—8% 1st° 14% 2nd° 8% 3rd°	1000 c.c. in 4 hrs. 1st day	Toxicity and general appearance markedly improved			Negative	Course in hospital complicated by pneumonia from which patient recovered
7-B† BB 31 yrs. Female 52-8523	75% burn—5% 1st° 10% 2nd° 60% 3rd°	3000 c.c. in 2 hrs. 1st day. 1000 c.c. in 4 hrs. 3rd day	Pulse, toxicity and urine output improved, with clearing of hemoglobin from urine complete in about 15 hrs. Improvement in hemoconcentration and toxicity with PVP on 3rd day		57.7 to 36.4% in 1 hr. Rise to 55.5% at 6 hrs. Hematocrit 74.5% 5 hrs. after 1st admin.	Cephalin flocculation 4 plus throughout hospitalization	Pt. died on 7th hosp. day in delirium tremens with severe toxicity and recurrent hemoglobinuria. Autopsy
8-B SB 41 yrs. Male 52-4335	40% burn—5% 1st° 15% 2nd° 50% 3rd°	3000 c.c. in 8½ hrs.	Pulse, toxicity, state of hydration and urinary output improved markedly	4454 to 4911 c.c. in 13 hrs.	57.9 to 46.9% in 8½ hrs. Rise to 47.6% at 42 hrs.	Negative	Patient discharged on 36th hosp. day. Resurfacing procedures without complication

*Plasma protein fell to 4.6 on 12th hospital day.
†Marked fall in serum protein to 2.85 on 5th day.

resurfacing impossible. The rapid development of contracture of the anterior neck and lower face not only made it difficult and uncomfortable for the patient to close her mouth but disposed to respiratory tract infection. In spite of frequent transfusions of blood and plasma, strict dietary management, parenteral nutritional supplements, antibiotics, and special nursing care, this patient developed a bronchopneumonia and expired on the seventy-ninth hospital day.

Laboratory data (Day plus days after admission):

3–16–52. Urine: Specific gravity 1.029; albumin, trace; sugar, negative. Benzidine test, strongly positive. Urine was dark port-wine in appearance.

3–24–52 (day plus 8). Urine: specific gravity, 1.012; albumin, negative; sugar, negative. Microscopic —few epithelial cells and few white blood cells; occasional mucus thread. Benzidine test, negative.

3–31–52 (day plus 15). Blood creatinine, 1.3 mgm.%; blood urea nitrogen 8 mgm.%; glucose, 93 mgm.%; hematocrit, 40%; total serum protein, 5.9 gm.%.

4–1–52 (day plus 16). Smear and culture of wound exudate, burned area; beta hemolytic streptococcus, B. coli, and B. proteus.

4–7–52 (day plus 22). Blood creatinine, 1.3 mgm.%; blood urea nitrogen, 8 mgm.%; blood glucose, 62 mgm.%; plasma chlorides 565 mgm.% as NaCl. Hemoglobin 72%; R.B.C. 3,500,000; W.B.C., 4,150. Urine: Specific gravity, 1,017; albumin, negative; sugar, negative. Microscopic —few epithelial cells.

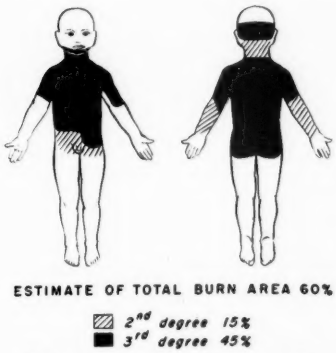

Fig. 1. Extent of burn in Case 4-B.

4–14–52 (day plus 29). Urine: Specific gravity, 1.017; albumin, 3+; sugar, negative. Microscopic—amorphous phosphate and triple phosphate crystals. Total protein, 5.65 gm.%; albumin, 3.4 gm.%; globulin 2.25 gm.%; A/G ratio, 1.51.

4–15–52 (day plus 30). Smear and culture from burn; alpha streptococcus, aerobacter aerogenes, B. proteus.

4–21–52 (day plus 36). Total protein, 3.9 gm.%; albumin, 2.4 gm.%; globulin, 1.5 gm.%; A/G ratio, 1.6. Hematocrit, 37.5%; hemoglobin, 104%; R.B.C. 5,000,000.

4–30–52 (day plus 45). Blood culture, sterile. Smear and culture from burn: B. proteus and Staphylococcus aureus (A) E. coli, Streptococcus viridans, Streptococcus fecalis.

5–16–52 (day plus 61). Hemoglobin, 56%; R.B.C., 3,660,000; W.B.C., 28,600, with 84% polymorphonuclears and young forms.

6–2–52 (day plus 78). van den Bergh, negative; cephalin flocculation, 3+. Blood creatinine, 1.3 mgm.%; urea nitrogen, 8 mgm.%; glucose, 66 mgm.%. Urine: specific gravity, 1,020; albumin, 1+; sugar, slight trace; acetone, negative. Microscopic—few epithelial cells; few oxalate crystals.

CASE 8-B. S.B., Hospital No. 52-4335. Total burn area 40 per cent. The patient was brought into the hospital 17 hours after his clothing caught fire while he was cooking over an open gas flame. He had been seen earlier in the hospital but signed out at his own responsibility, without accepting treatment except to have the burns dressed. There was a past history of chronic alcoholism, with an alcoholic bout in progress at the time of injury. There was no history of other acute or chronic illnesses with a bearing upon the present condition. The patient had been treated for lues many years before.

Physical examination showed: a blood pressure of 132/94; pulse rate of 140 per minute, poor quality; respirations were 24 per minute; temperature was 101.8 degrees F. The patient was a large well developed, well nourished (83.4 kgm.), 41 year old colored male in acute distress, dehydrated, restless,

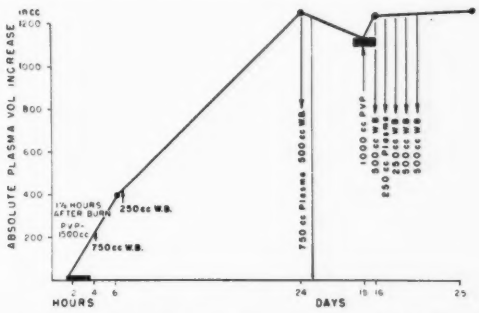

Fig. 2. Shock due to 60 per cent second and third degree burns. Curve shows increase in absolute plasma volume with initial infusion of 1,500 cubic centimeters PVP-macrose (indicated by bar on abscissa), followed by transfusion of 750 and 250 cubic centimeters of whole blood (W.B.), at the indicated times during the first 24 hours. A second increase in plasma volume after PVP-macrose is also shown on the fifteenth hospital day.

seemingly irrational at intervals, complaining of moderate pain and severe thirst, demanding water and vomiting it immediately, although only small amounts were given. The extent of the burn is shown in Figure 3. On examination the head was normal; pupils, equal, slightly dilated, but reacted to light and convergence. No evidence of significant burn of oropharynx was present. Lung fields were clear to auscultation. The heart was very rapid and sounds of poor quality; no murmurs. Abdomen was moderately obese; no masses or organs were felt. The skin of the extremities was burned as shown, otherwise the extremities were negative.

A total of 3,000 cubic centimeters of PVP was given in approximately 8½ hours, during which time the toxicity, the quality of the pulse, and the skin turgor showed improvement. The hematocrit

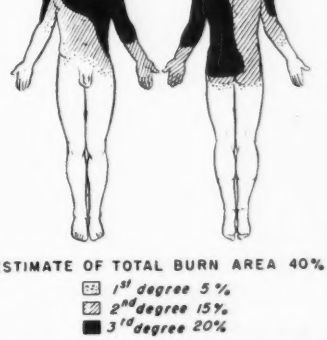

Fig. 3. Extent of burn in Case 8-B.

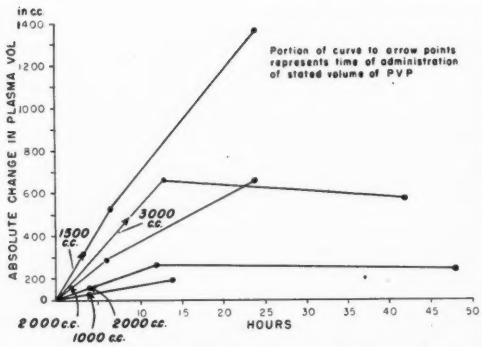

Fig. 4. Absolute plasma volume changes after administration of PVP in severe burn cases. These curves from above downward represent the plasma volume changes occurring in Case 4-B (first administration), Case 8-B, Case 5-B, Case 1-B, and Case 4-B (second administration), respectively.

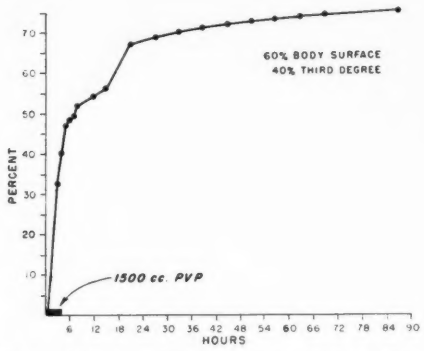

Fig. 5. Urinary excretion curve of PVP in Case 4-B after first infusion of PVP-macrose.

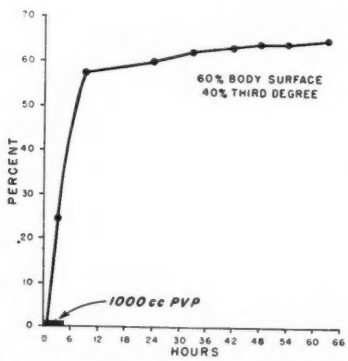

Fig. 6. As in Figure 5 after second infusion of PVP-macrose.

fell from 57.9 to 46.9 per cent. The urine output remained satisfactory, and the patient was generally improved. The persistent vomiting made it impossible to give the patient food, and for the first 3 days, he received intravenous fluids: glucose and saline, Ringer's lactate, amigen, alcohol and glucose solutions, with high vitamin supplement, and 1 transfusion of 500 cubic centimeters of plasma. The patient complained of weakness, although his sensorium remained clear, and the urine output good. Some portions of the burn showed signs of infection. On the fifth hospital day the patient received the first blood transfusion, and thereafter, blood and plasma transfusions were frequent. The severe anorexia and nausea gradually subsided during the second week of hospitalization. Thereafter the patient took a high protein diet fairly well, and the resurfacing procedures were performed without complication. The patient was discharged from the hospital on the fifty-sixth hospital day, still convalescent, but able to be followed in clinic.

Laboratory data (day plus days after admission):

3–16–52 (date of admission). Blood, type B, Rh+. Urine: clear, dark amber in color, specific gravity, 1.026; albumin, negative; sugar, negative. Benzidine test, negative.

3–17–52 (day plus 1). Blood creatinine, 1.3 mgm.%; blood urea nitrogen, 14 mgm.%; blood glucose, 135 mgm.%; serum van den Bergh, negative. Cephalin flocculation, negative. Total serum proteins, 4.2 gm.%; A/G ratio, 1.9. Serum Kolmer, 1+; VDRL, 1+.

3–19–52 (day plus 3). Total serum proteins, 5.30 gm.%; albumin, 4.2 gm.%; globulin, 1.1 gm.%; A/G ratio, 3.82. Alkaline phosphatase, 3.4 Bodansky units.

3–21–52 (day plus 5). Total serum proteins, 5.9 gm.%; albumin, 3.4 gm.%; globulin, 2.5 gm.%; A/G ratio, 1.36. Blood creatinine, 1.3 mgm.%; blood urea nitrogen, 14 mgm.%; blood glucose, 135 mgm.%.

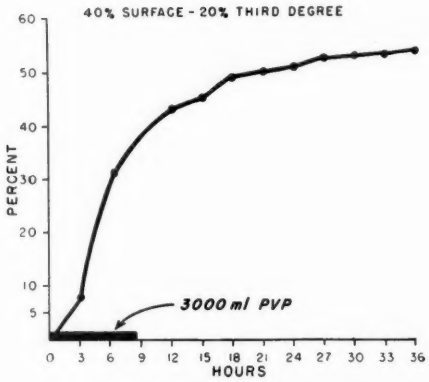

Fig. 7. Urinary excretion curve of PVP in Case 8-B

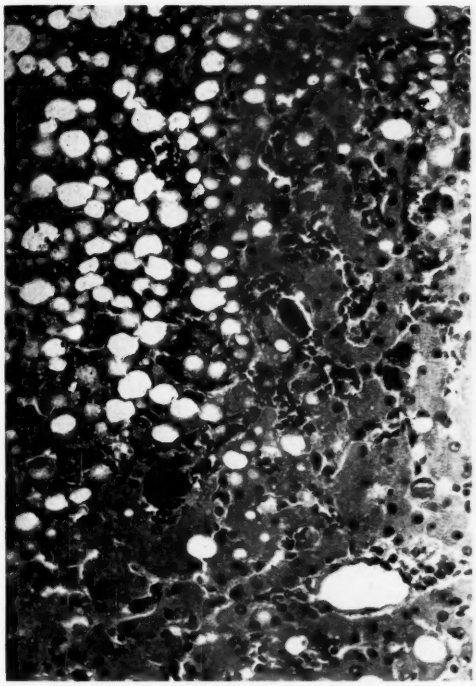

Fig. 8. Case 4-B. Section of liver, showing extensive fatty degeneration and large numbers of giant sized Kupffer cells in the sinusoids. Some of these cells are multinucleated and vacuolated, and contain globules of basophilic material. Hematoxylin and eosin stain, ×125.

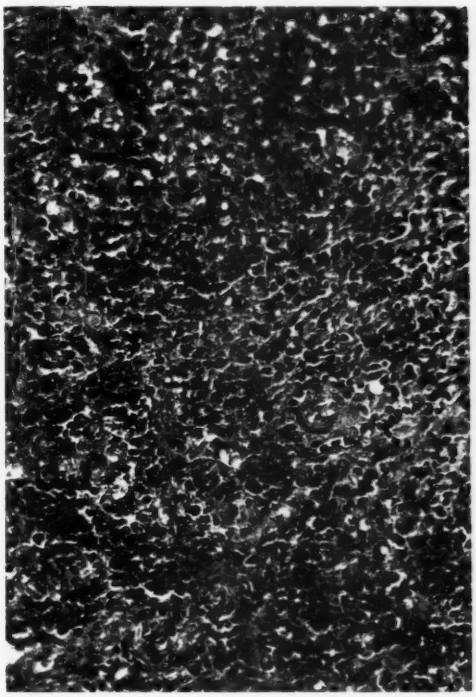

Fig. 9. Case 4-B. Section of spleen, showing numerous small fragments of hemosiderin and a few macrophages containing a basophilic material similar to that noted in the liver. ×125. Some of the basophilic material also appears to be extracellular in location.

3–24–52 (day plus 8). Total serum proteins, 5.9 gm.%; albumin, 4.3 gm.%; globulin, 1.6 gm.%; A/G ratio, 2.68. Carbon dioxide combining power, 62 vol.%. Blood creatinine, 1.3 mgm.%; blood urea nitrogen, 9 mgm.%; glucose, 110 mgm.%. Urine: Clear amber in color; specific gravity, 1.000; albumin, negative; glucose, negative. Microscopic—occasional epithelial cell. Serum Kolmer, 1+. VDRL, 1+.

3–31–52 (day plus 15). Serum van den Bergh, negative; cephalin flocculation, negative. Total serum proteins, 7.7 gm.%; albumin, 3.9 gm.%; globulin, 3.6 gm.%; A/G ratio, 1.46. Alkaline phosphatase, 4.9 Bodansky units.

4–2–52 (day plus 17). Total serum proteins, 7.5 gm.%; albumin, 4.45 gm.%; globulin, 3.05 gm.%; A/G ratio, 1.46. Alkaline phosphatase, 4.9 Bodansky units. Wound culture: gamma streptococci, B. proteus, and paracolon bacilli.

4–18–52 (day plus 33). Blood creatinine, 1.3 mgm.%; blood urea nitrogen, 11 mgm.%; blood glucose, 155 mgm.%. Wound culture: alpha streptococci, B. coli and alcaligenes faecalis.

4–24–52 (day plus 39). Hemoglobin, 94%; R.B.C. 4,600,000; W.B.C., 9,700. Urine: specific gravity, 1,010; albumin, trace; sugar, negative. Microscopic—few white blood cells, epithelial cells, and mucus threads. Total serum protein, 6.5 gm.%; albumin, 3.5 gm.%; globulin, 3 gm.%; A/G ratio, 1.16.

5–2–52 (day plus 47). Total serum proteins, 6.8 gm.%; albumin, 3.2 gm.%; globulin, 3.6 gm.%; A/G ratio, 0.89.

DISCUSSION

This group of cases includes 4 males and 4 females, with ages ranging from 4 to 54 years. The areas involved by the burns varied from 20 to 75 per cent of the body surface as estimated by the method of Lund and Browder. Volumes of PVP from 1,000 to 3,000 cubic centimeters were infused in periods of time from 1 to 8½ hours.

In all cases treated with PVP on admission there was definite recovery from shock, decrease in hematocrit, improvement of toxicity, and increases in urinary output. In 3 cases the gross hemoglobinuria cleared in periods of 12, 15, and 48 hours respectively (Cases 4, 7, and 5). The improvement of the patient and the fall in hematocrit were not maintained as well as in the hemorrhagic and traumatic shock. This is readily understood by the large and continued fluid and protein loss from the burned areas. The fall in hematocrit and the dilution of the peripheral blood and plasma were, in turn, followed by a secondary rise to approximately their initial levels, in periods of 6 to 36 hours, depending on the severity and extent of the burn. In no case did we fail to observe immediate improvement with fall in hematocrit. Of the 4 patients in this series who succumbed, none died from early burn shock, hemoconcentration or toxicity (Cases 3, 4, 5, and 7).

The blood volumes measured in Cases 1, 4, 5, and 8 revealed definite increases in 6 to 48 hours following administration of PVP-macrose (Fig. 4). No significant alteration in blood electrolytes followed infusions of PVP.

The urinary excretion curves showed a similar pattern (Figs. 5, 6, and 7), with an early rapid loss of PVP, which later tapered off. Within 24 hours approximately 50 to 70 per cent of the infused material appeared in the urine.

Three patients with laboratory evidence of impairment of liver function died (Cases 3, 4, and 7). The foamy appearance of the Kupffer cell cytoplasm, and the bluish inclusion material seen microscopically in both liver and spleen at necropsy in Case 4 (Figs. 8 and 9) are in agreement with the previously reported findings of Schoen. Microscopic study of the tissues of the other patients who died did not reveal these inclusions. In 4 patients, one of whom died (Case 5), there was no laboratory evidence of impaired liver function.

A sharp plasma protein decrease occurred in 2 patients (Cases 5 and 7). This may be related to the PVP therapy, coupled with the losses from the burn, and impairment of liver function. Heilmeyer and Weese have presented evidence that whenever the circulating plasma is made slightly hyperosmotic with an infusion of PVP, or when PVP is administered in states of protein depletion (as in burns), the plasma albumin is decreased by an amount equivalent oncotically to the PVP in the plasma. This factor may have been in operation in the 2 cases cited in which plasma albumin values fell to 2.05 grams per cent and 1.6 grams per cent on the twelfth and fifth hospital days respectively (Cases 5 and 7), suggesting that early hypoproteinemia must be watched for and guarded against in using PVP-macrose in these cases.

CONCLUSIONS

1. Polyvinylpyrrolidone has been used as initial intravenous therapy in 8 severe burn cases.

2. Clinical responses have been good, as evidenced by improvement in blood pressure, pulse, burn toxicity and vital signs, fall in hematocrit, blood and plasma specific gravities, and increase in urinary output with clearing of hemoglobinuria in 3 cases.

3. There was no evidence of toxicity referable to the PVP administered. One apparent reaction after a PVP infusion seemed more likely to be due to the increase in blood volume with toxins from burned areas drawn into the blood stream.

4. The decrease in serum albumin must be watched for, and guarded against, with adequate diet, intravenous plasma, albumin, and blood transfusions along with early skin grafting.

5. Our results substantiate previously published experiences and indicate that PVP is a valuable adjunct in the early treatment of burns.

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THE HISTOGENESIS OF SQUAMOUS CELL METAPLASIA OF THE CERVIX AND ENDOMETRIUM

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SINCE the term "epidermidalization"[1] was coined in the early 1880's to describe the transformation of areas of cylindrical epithelium of the human cervix uteri into squamous epithelium the subject has been discussed by a great many investigators. Its possible association with malignancy has been mentioned repeatedly, but it is primarily of a purely benign nature. It has been described not only in the cervix but also in the endometrium, and at all times from intrauterine life to old age. Several complex theories have been advanced to explain the manner in which it is brought about, but there is no uniformly accepted explanation.

The extensive distribution of epidermidization and the ease of reproducing similar microscopic lesions in experimental animals suggest that the origin actually is of a simple nature. The present communication is advanced in support of the concept that epidermidization is an indirect metaplastic process by which immature cells are derived from normal cylindrical epithelium and develop into stratified squamous epithelium.

EPIDERMIDIZATION

The various steps by which a surface covered by cylindrical epithelium is transformed into stratified squamous epithelium are well known, and many articles on the subject are accompanied with excellent sketches and photomicrographs. The first stage is characterized by the appearance, beneath the cylindrical cells and above the basement membrane, of a single row of distinctive cells the origin of which is the key to our understanding of the whole process (Fig. 1a). These cells have been described under various names such as "basal cells," "subcylindrical basal cells," "infraepithelial cells," and "reserve cells." They are small, polygonal in shape, stain deeply, and the nuclei are round or oval. They are regularly arranged, and their general appearance suggests the basal cell layer of squamous epithelium. They must be considered as elements capable of differentiating into either squamous or columnar cells or into cell forms which combine the characters of both cell types. Carmichael and Jeaffreson (5) were able at times to demonstrate the presence of granules of mucin in their cytoplasm by special staining methods, and individual cells overdistended with mucous secretion are a frequent occurrence.

During the early stage of epidermidization these basal cells proliferate and form a stratified layer of from 2 to 8 or more rows which elevate the cylindrical cells from the basement membrance (Fig. 1b). At first the cylindrical cells remain normal in appearance but eventually they are cast off, and the proliferating new cells undergo a process of differentiation (Fig. 1d). They become larger, their outlines more distinct, the cytoplasm does not stain as deeply, and they assume a rectangular shape so that the resultant tissue is not unlike the transitional epithelium of the bladder and urethra. The lowermost cells, which represent the active proliferating portion, remain small and polygonal. The cells at the surface finally become longer and flattened, cornified, and the differentiation progresses to normal stratified squamous epithelium with its three distinct layers.

Epidermidization occurs not only on free surfaces but also deep in glands, and many extraordinary pictures may be presented by the various transitional phases (Fig. 2). The proliferating cells may form irregular masses

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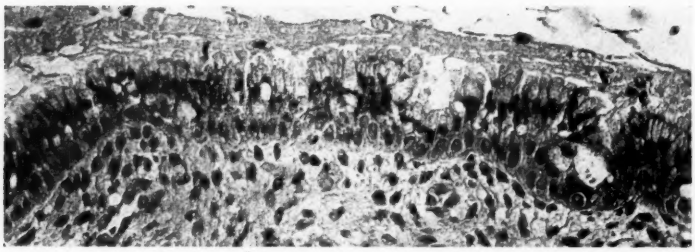
[1]The term "epidermidalization" has since been simplified to "epidermization" and "epidermidization." "Epidermoidalization" is applied to the bizarre patterns produced by the stratification of basal cells with vacuolated inclusions and especially when they are present in glandular structures.



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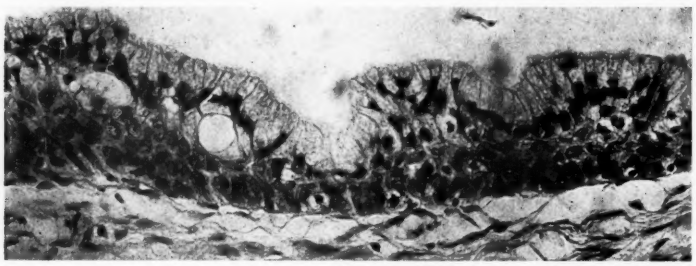

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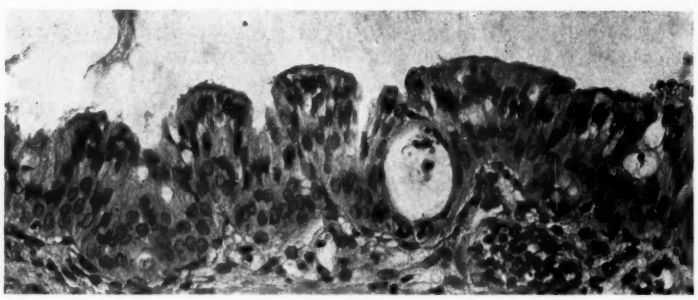

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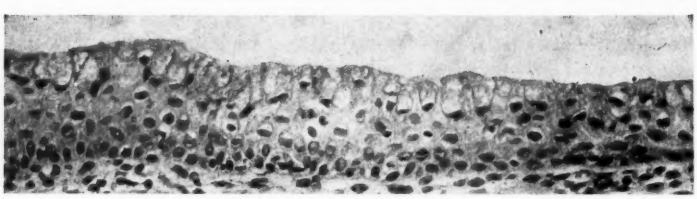

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Fig. 1. Early stages of epidermidization of the cervix uteri, illustrating the appearance of the so-called "basal," "infraepithelial," or "reserve" cells. Section c is from a mucous polyp. × 220.

which project into and even completely fill the gland lumina. Since they have the capacity of forming mucus they may become overdistended with secretion, giving the tissue a peculiar "fenestrated" or "vacuolated" appearance, the so-called "mucoid degeneration" or "epidermoidalization" of older authors. The bizarre formations which may

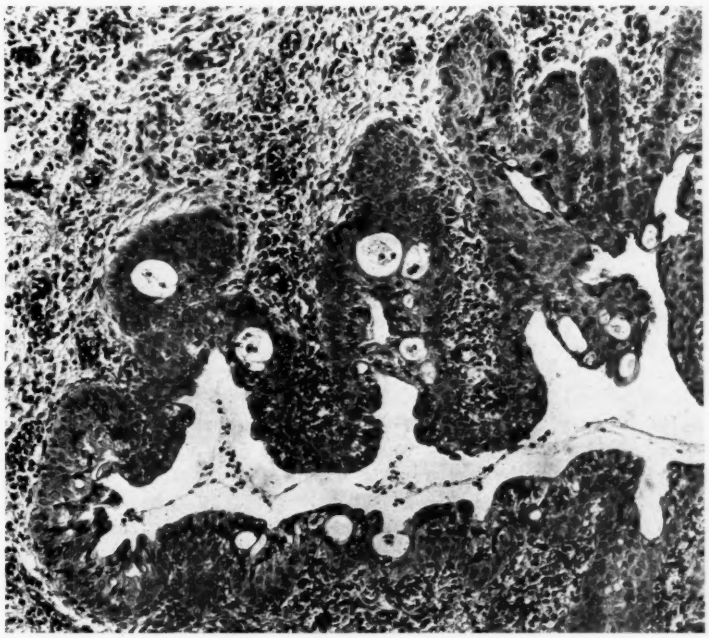


Fig. 2. Epidermidization in glands of a mucous polyp of the cervix uteri. Attention is directed to the cells distended with mucoid secretion. Once known as "epidermoidalization," this histologic picture has been confused with carcinoma. × 112.

result from these various changes are very important in differential diagnosis and many times have been mistaken for carcinoma. It also should be emphasized that epidermidization must not be confused with hyperplastic and anaplastic changes in basal squamous epithelial cells, nor with so-called carcinoma in situ.

The process of epidermidization may take place over a considerable area but more often it originates in isolated patches and in widely separated individual glands. The result is that different fields from the same specimen show all phases from the early appearance of a single row of the small basal cells to complete stratified squamous epithelium.

A number of recent studies of the histologic appearance of the cervix uteri during pregnancy by Carrow and Greene, Rosenthal and Hellman, and Nesbitt and Hellman apparently depart from the classic description of epidermidization and reserve this term for the late stages with more definite differentiation into squamous epithelium. The early stages when the cylindrical epithelium is undermined by the basal cells are referred to as "stratified cylindrical epithelium" in spite of the fact that only the surface cells are cylindrical. The glandular changes once known as "mucoid degeneration" or "epidermoidalization" also are called "adenomatous hyperplasia" or "hyperactive glandular epithelium." The implication that these represent processes distinct from the different stages of epidermidization awaits clarification.

DISTRIBUTION

A complete bibliography of the older literature on the distribution of epidermidization will be found in two of my former reviews (11, 12). It will be noted that the many papers on the subject invariably have dealt with its occurrence either in the cervix or in the endometrium, and as an accompaniment of some specific physiologic or patho-

logic condition. It consequently has been described as a lesion varying in its manifestations according to its location. This is unfortunate because in seeking an explanation for its origin it would be desirable to regard it as a basic histologic process. It is important, not only for the present analysis but also in cancer studies, to find an explanation applicable under all circumstances.

Cervix uteri. The cervix presents the most fertile field for study, and here epidermidization occurs both on the portio vaginalis and the cervical canal. Carmichael and Jeaffreson (5) observed congregations of the basal cells in 95 per cent, Auerbach and Pund in 72 per cent, and Howard, Erikson, and Stoddard in 83 per cent of cervices examined. More advanced stages of epidermidization were noted in over 40 per cent of cases in a large series by Carmichael and Jeaffreson (5), in 33 out of 579 cervices in another by Schottlaender, and again by Fluhmann (11) in 59 out of 1,195 specimens of the cervix.

Various degrees of epidermidization are found in the cervix during intrauterine life, in the newborn, and during pregnancy.

It occurs as an important histologic process in erosions of the cervix, especially in the "second healing stage," and in mucous polypi. In one series of 100 polypi Fluhmann (10) observed epidermidization in 29 cases, and Mezer in 31 per cent of another 1,636 specimens.

Carcinoma cervicis uteri. Some of the earlier authors considered epidermidization as definitely carcinomatous, and to others it was a "precancerous lesion." Its benign character is now recognized, but a possible relationship with malignancy has aroused considerable discussion. At any rate it does occur as a benign accompaniment of cervical adenocarcinoma.

Endometrium. Squamous epithelium in the endometrium is well recognized and most instances show a fully developed epithelium. There are, however, examples which illustrate all the steps of epidermidization from the early appearance of the basal cells to stratification, differentiation into layers, and keratinization. The older authors employed the terms "psoriasis uteri," "leucoplakia uteri," and "ichthyosis uteri," while "epidermidization" has been in general usage for the process in the endometrium as well as in the portio vaginalis and the endocervix.

The first report of epidermidization associated with endometritis was published by Zeller in 1884, but was met with considerable skepticism. However, this observation was subsequently corroborated, and it has been described at all ages and associated with many pathologic conditions. During regeneration of the uterine mucosa following curettage a tissue resembling squamous epithelium has been observed. Among lesions characterized by the occasional occurrence of epidermidization are pyometra, tuberculosis, following intrauterine applications of formalin, sarcoma, and chronic inversion of the uterus.

It has been found in the newborn, in a child 5 months old who died from a deficiency of vitamin A, in children before the age of 3 years, and in old age.

The occurrence of epidermidization on the surface and in the glands of endometrial polypi is significant in any discussion of the mechanism concerned with this transformation. The finding of squamous epithelium in hyperplasia endometrii is of particular interest, and in one series Fluhmann (13) observed it twice out of 75 cases. Sometimes it is manifested as isolated islands of squamous epithelium which, according to R. Meyer (27) represent cords of cells emanating from basal cells underlying surface cylindrical epithelium.

Carcinoma fundus uteri. It was inevitable that from the first the relationship between endometrial epidermidization and carcinoma should hold interest. Since the present contribution does not purport to discuss this problem it seems sufficient to quote from my previous review (12) the four circumstances under which squamous epithelium in the endometrium is found associated with carcinoma: (1) squamous epithelium occurring as a metaplastic process in an adenomatous carcinoma of the uterine cavity; (2) squamous cell carcinoma coexisting with an adenocarcinoma; (3) squamous cell carcinoma of the corpus secondary to a similar growth of the cervix uteri; (4) primary squamous cell carcinoma of the uterine body.

The limitations of space prevent a detailed account in this report of squamous metaplasia in other organs besides the uterus. However, it has been observed particularly in various ducts and usually associated with chronic inflammatory lesions. Its occurrence is notable with chronic bronchitis, bronchiectasis, pyelonephritis, and in bladder, larynx, gallbladder, and pancreatic and prostatic ducts.

THEORIES OF ORIGIN

Epidermidization is a fundamental histologic process and it is desirable to seek an explanation for its histogenesis that would be generally applicable irrespective of its site or of accompanying lesions. Any theory for the origin of epidermidization must explain the source of the so-called "basal cells," "infraepithelial cells," or "reserve cells." Their appearance beneath the cylindrical epithelium is the first stage in the transformation which eventuates into stratified squamous epithelium. Although once considered as derived from stromal cells it is now agreed that they are of an epithelial nature and arise above the basement membrane. For purposes of discussion the various theories for the genesis of these basal cells may be grouped into three important categories: (1) cells derived from squamous epithelium; (2) fetal or embryonic cells (a) fetal squamous epithelial cells, (b) undifferentiated cellular rests; (3) cells derived from cylindrical epithelium (a) direct metaplasia, (b) indirect metaplasia.

Cells derived from squamous epithelium. One of the simplest explanations for the origin of the infraepithelial cells is that they represent an ingrowth of basal cells from adjacent normal squamous epithelium. This concept was advanced by Eichholz and has received support from many authorities such as R. Meyer (25), Frankl, and Novak (30). Its chief application has been in Robert Meyer's interpretation of the various stages of cervical erosions and most of us have been brought up on this teaching.[1]

[1]Somewhat related to this theory is the suggestion that epidermidization may occur as a direct implantation, for instance on a mucous polyp projecting from the external os. As Meyer (26) states, however, this possibility is so limited by exceptions that it is not acceptable.

There is no denying that a surface denuded of its epithelium as a result of trauma or inflammatory ulceration may be covered by an extension of adjacent tissue. It is a fundamental finding in wound healing, and is applicable to both cylindrical and squamous epithelium. But this process should be considered as "epithelialization," *not* "epidermidization."

The proponents of this theory, however, also explain the presence of the cells underlying cylindrical epithelium in the first stage of epidermidization as representing an invasion by the basal cells of neighboring squamous epithelium.

There are several objections which render this theory invalid for general application. First, it assumes that the process represents a horizontal progress of basal cells extending from normal squamous epithelium to underlie the cylindrical cells and dislodge them. In other words, under certain conditions these basal cells must acquire invasive properties akin to cancerous tissue. However, the appearance of well preserved cylindrical units above several rows of basal cells is against the concept of a destructive invasion which would necessarily disrupt the nutrition of the surface elements. In cancerous extension the cylindrical cells are rapidly cast off in a necrotic form, but in epidermidization they persist in a healthy state until late in the process (Fig. 1a, b, c). Second, there is no experimental evidence for such an extension of squamous basal cells, and it is just as likely that the order of growth is vertical and not horizontal, with the basal cells (of epidermidization) originating directly below the cylindrical cells and extending outwards. Third, a clear-cut line of demarcation between normal squamous epithelium and the atypical multilayered area is against the concept that one is an extension of the other. Fourth, the basal cells sometimes contain granules of mucin, a characteristic of cylindrical, not squamous, epithelium. Fifth, epidermidization often occurs in areas of the cervix where there is no adjacent squamous epithelium, such as isolated patches on the surface, in mucous polypi, and deep in individual glands. Sixth, it is inapplicable to

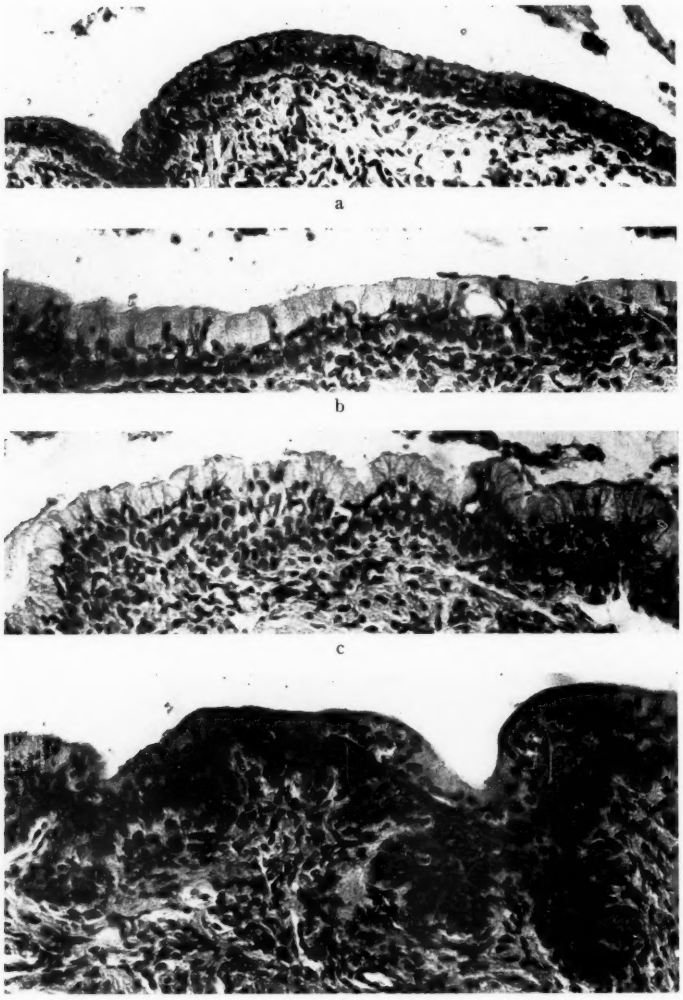


Fig. 3. Stages in the "mucification" of the vagina of the spayed mouse. It is not only a stage in the production of cornification, but the end effect of subminimal doses of estrogen. Attention is directed to the similarity with early epidermidization of the human cervix uteri (Fig. 1). × 220.

epidermidization originating in the endometrium near the fundus uteri.

Derivation from fetal or embryonic cells. Fetal squamous epithelial cells.—In his studies on the development of the epithelial covering of the cervix and his theory for the formation and healing of erosions, Robert Meyer (24, 25, 26) postulated an explanation for the development of epidermidization where ingrowth from adjacent squamous epithelium is not possible. He showed that in the third to fourth month of fetal life the undifferentiated cellular covering of the portio develops into squamous epithelium

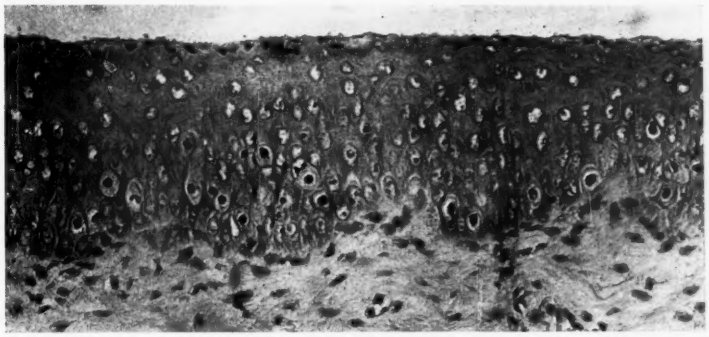


Fig. 4. Late stage in the transformation of the low cuboidal epithelium of the spayed mouse vagina into cornified squamous epithelium. The actual proliferation occurs in the basal cells, as evidenced by mitotic figures. This section is from the vagina of a spayed mouse given 0.1 milligram of stilbestrol subcutaneously 48 hours before autopsy. Colchicine administered 9½ hours before the animal is sacrificed holds the mitoses in the metaphase (Dustin's technique). × 220.

which extends high up into the cervical canal. At about the sixth month cylindrical epithelium appears and gradually forces the squamous epithelium out of the canal. In this transition a certain number of basal cells are left beneath the cylindrical epithelium, where they remain latent until some future time when under the influence of an unknown stimulus they grow and supplant the overlying cells as in epidermidization.

Obviously, this theory cannot account for epidermidization in locations not covered with squamous epithelium during fetal life. Some of the objections advanced for the other theories also may be raised. For instance, it is necessary for its acceptance to presuppose a horizontal advance of cells; this progression does not explain adequately the association of epidermidization with cancer; the incidence of such "fetal cells" would be inordinately high; and it is difficult to conceive of their persistence for such long periods of time.

Undifferentiated cellular rests.—This explanation depends on the belief that certain embryonic undifferentiated cells from the primitive lining persist as inclusions in cylindrical epithelium. These units supposedly contain in themselves the potentialities of developing into either type of tissue and mature into squamous epithelium following a pathologic stimulus such as inflammation. This possibility was discussed by Eichholz as long ago as 1902, and it has received support from Geller, Carmichael and Jeaffreson (4), Pund and Auerbach, Howard, Erikson and Stoddard, and Rosenthal and Hellman. The term "reserve cell" was adopted during the course of such studies. Novak (31) and Faulkner and Douglas assert that in adenoacanthoma of the uterus the squamous elements of the growth are not malignant and arise from "indifferent" cells.

The objections to this theory are of a fundamental nature. (1) The basal cells which lead to squamous epithelium have been found in from 70 to 95 per cent of all cervices. This high incidence is much more in favor of a normal tissue constituent than an abnormal cellular inclusion.[1] (2) There is no proof that the basal cells are truly embryonic in character; this concept is purely an assumption. (3) There is no assurance that such cells, if embryonic, would always lead to normal squamous epithelium. (4) Although the basal cells are of great frequency teratomatous newgrowths are very rare in the uterus. (5) It is difficult to conceive that undifferentiated cells may make their appearance as an additional character-

[1]Krompecher insisted that cylindrical epithelium has a basal cell layer, but he considered it as having an embryonic character and able to differentiate into squamous epithelium. Such a process he termed "regenerative dysplasia."

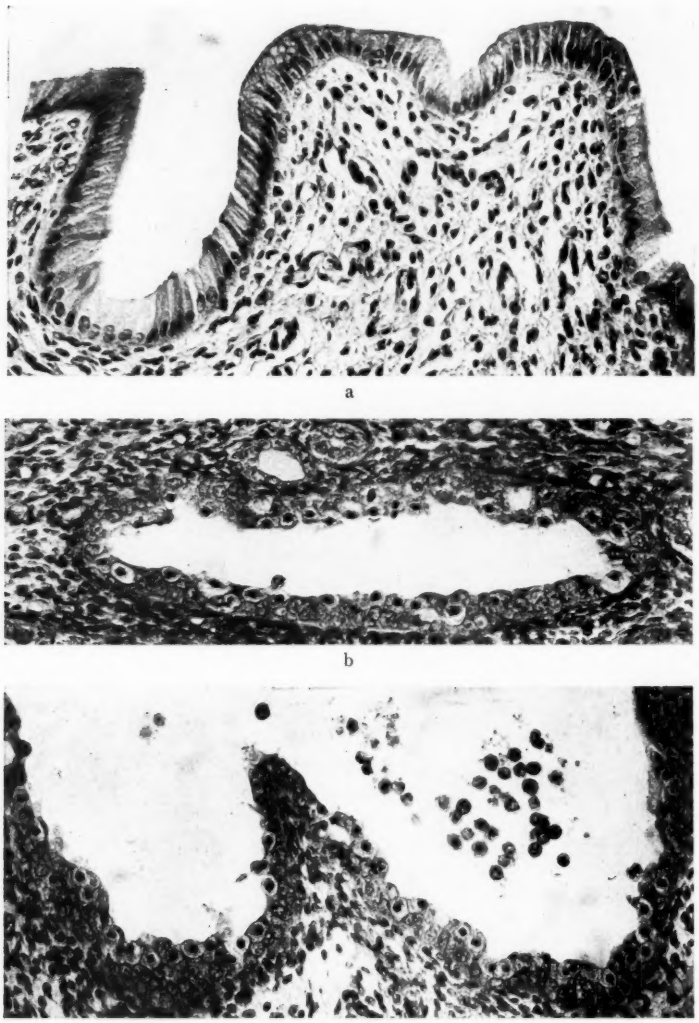
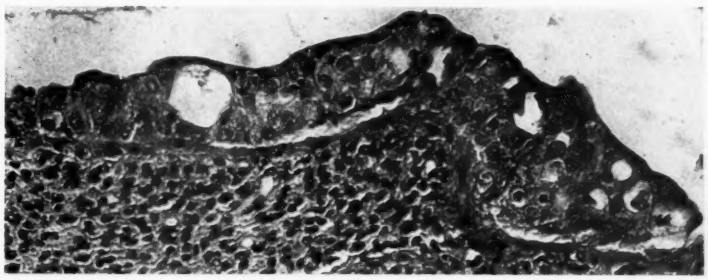


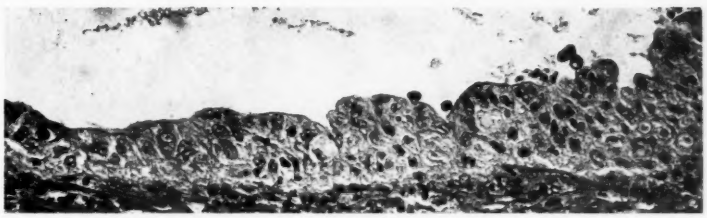
Fig. 5. Tall cylindrical epithelium of the rat endometrium (a). The injection of 0.1 milligram of stilbestrol subcutaneously in mouse or rat is followed in 24 hours by the appearance of numerous mitotic figures (b, c). × 220.

istic of newgrowths such as mucous polypi of the cervix, endometrial polypi, and adenocarcinoma. (6) It requires some stretch of the imagination to accept the persistence of cellular remnants of a blastemic character for 20, 30, or 40 years in a tissue such as the endometrium which is cast off completely, except for its basal layer, and regenerated at monthly intervals during that whole period.

Cells derived from cylindrical epithelium. Direct or true metaplasia.—The conversion of mature cylindrical cells directly into stratified squamous epithelium was once considered but there is no histologic evidence for



a



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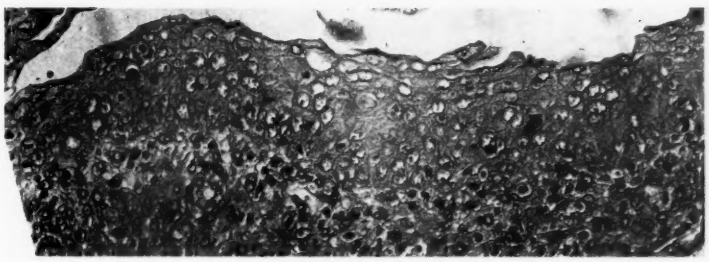


c

Fig. 6. Various stages in the squamous metaplasia of the mouse endometrium following the prolonged administration of estrogenic hormone. These mice were given 0.1 milligram of stilbestrol subcutaneously three times weekly. Section a is from a mouse injected in this manner for 21 days, and b and c from an animal treated for 67 days. × 220.

this change and it is no longer tenable as a possibility.

Indirect metaplasia, or prosoplasia.—The theory which maintains that the basal cells concerned with epidermidization are derived from normal cylindrical epithelium remains as the only one free of the various objections raised for the other explanations. It was suggested in 1906 by Kaufmann and Oeri, and in 1914 by Carl Ruge II, who believed that the infraepithelial cells represented various transitional phases of a metaplastic process. Among modern authors it is accepted as applicable to the endometrium but only at certain times in the cervix.

The location of the basal cells of epidermidization, their content of mucin granules, the mucoid degeneration seen at various stages, speak in favor of their origin from cylindrical cells. It affords an explanation for the survival of the surface cylindrical cells during the early stages since they remain an integral part of the whole epithelium and receive an adequate capillary and lymphatic supply. This concept also is applicable to epidermidization occurring in all

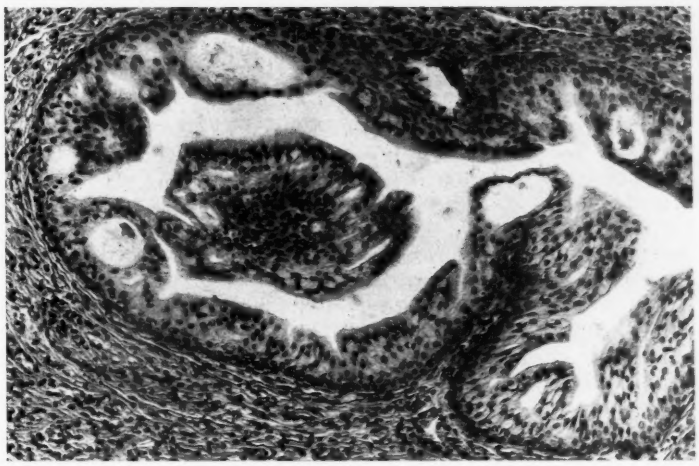
Fig. 7. Cornification of uterine cavity of a normal rat injected daily with a preparation of chorionic gonadotrophic hormone for 272 days. × 112.

parts of the cervix and endometrium, and in newgrowths such as cervical polypi, endometrial polypi, and adenocarcinoma. However, it becomes necessary to demonstrate that such cells can mature into either or both cylindrical and squamous elements. The answer has not been found in histologic studies in the human, but the behavior of the lining epithelium of the vagina and uterus of the laboratory mouse and rat indicates that this type of cell transformation does occur in these animals under normal and experimental conditions.

EXPERIMENTAL ANIMALS

The transformation of cylindrical epithelium into squamous epithelium in the uteri of experimental animals has been accomplished many times. It has offered an excellent controlled source for studying the manner in which epidermidization can be brought about. As long ago as 1900 d'Erchia observed this type of metaplasia after ligating a uterine horn in pregnant guinea pigs and causing a retention of products of conception for a period of 2 months. Wolbach and Howe produced an extensive keratinization of the uterine cavity in rats fed a diet lacking in fat soluble vitamin A. The prolonged administration of estrogenic hormone resulted in various stages of epidermidization in the uteri of rats in the hands of Selye, Thompson, and Collip, McEuen, Korenchevsky and Hall, and others, and of mice by Lacassagne. In the Stanford Gynecological Laboratory this process was seen by Fluhmann (15) in normal rats following the prolonged injection of chorionic gonadotrophic hormone.

a



b

Fig. 8. Epidermidization, with inclusions of cells distended with mucus, of the uterine glands in a normal rat injected daily with chorionic godatrophin for 365 days. Attention is directed to its similarity with "epidermoidalization" (Fig. 2) in the human cervix uteri. × 112.

Other unusual histologic changes have been noted after the injection of androgenic hormone and in spayed and hypophysectomized animals subjected to various laboratory procedures. The stages which accompany the development of cornified epithelium in the vaginas of spayed mice have been observed in over 5,000 animals used in the Fluhmann "mucification test" for estrogen (14). For the purpose of illustrating this report and to study the occurrence of mitotic figures in the vagina and uterus a group of 12 adult spayed mice were given 0.5 milligram of stilbestrol subcutaneously 3 times weekly. They were sacrificed at intervals from 1 to 67 days, and given 0.5 cubic centimeter of a 2 per cent solution of colchicine subcutaneously 9½ hours before autopsy. This method (Dustin's technique) is an excellent way of demonstrating active tissue growth as it holds in the metaphase all cells undergoing mitotic division.

Within a few days after castration the mucosa of the rat or mouse vagina consists of 1 or 2 layers of low cuboidal cells, and under the influence of estrogenic hormone it

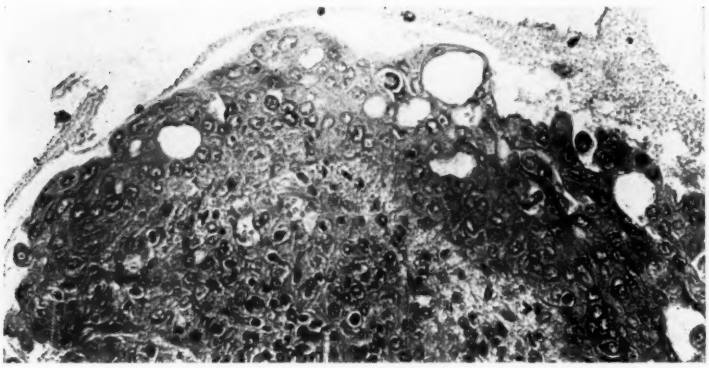


Fig. 9. Incomplete epidermidization of the uterine cavity in the mouse, with cells distended with mucus. From the same specimen used for Figure 6b and c. × 220.

passes through certain stages which closely simulate epidermidization in the human uterus. The first stage in this transformation is an active growth of the lining cells which assume a definite arrangement into 2 layers (Fig. 3a). The surface cells become tall secreting cylindrical cells (Fig. 3c, d), and the resultant picture is comparable to the descriptions of the human cervix where the cylindrical epithelium is found undermined by the basal cells (Fig. 1a, b, c).

There now follows a proliferation of the lowermost cells until they are arranged into 2 to 8 layers with a single row of cylindrical cells at the surface, also very similar to stages of epidermidization in the human. This formation in the rodent vagina is known as "mucification" and is not only a stage in the production of cornification but the end effect of subminimal doses of estrogen. It also may be evoked by androgens and by mixtures of estrogen and progesterone. Under normal conditions it is found in immature animals at the time of opening of the vaginal introitus, as well as during pseudopregnancy and pregnancy.

The next step in the transformation of the rodent vagina under estrogen stimulation is a disintegration and casting off of the surface cylindrical cells, a hypertrophy of the underlying cells, and a gradual flattening and keratinization or cornification at the surface (Fig. 4). At this time colchicine studies indicate that actual proliferation of the cells is only found in the basal cell layer of the resultant squamous epithelium (see mitotic figures in Fig. 4). The cornified cells are thus clearly descendants of the original basal cells.

However enlightening these changes may be, the criticism remains that the original surface epithelium of the vagina is not composed of tall cylindrical cells as in the human. However, epidermidization can be produced in the rat and mouse uterus which is normally lined by cylindrical epithelium (Fig. 5 a) and contains glandular structures. The individual stages are not as definite as in the vagina but the end result is the same. This change also is difficult to induce and sometimes requires injections over long periods of time. In our laboratory this type of indirect metaplasia has been seen in spayed mice receiving estrogen over many weeks, and was reported by Fluhmann (15) in intact rats given chorionic hormone daily for as long as 365 days.

A maximal growth activity of the rat or mouse endometrium is best demonstrated with colchicine 24 to 48 hours after the first injection of estrogen, as first reported by Allen, Smith, and Gardner. It is seen from Figure 5b, c that there is a tremendous mitotic activity and in time the cells hypertrophy, become stratified, and assume characteristics of either cylindrical or squamous cells at the surface. These changes occur at various degrees of intensity in different areas

(Figs. 6a, b, c; 9), until eventually the whole uterine cavity may be lined with cornified squamous epithelium (Fig. 7)[1]. Various formations due to the inclusion of cells distended with mucus also occur, especially in glands, and simulate the picture of "epidermoidalization" in the human cervix (Figs. 8, 9).

The application of observations directly from one species to another is fraught with possibilities for error. Nevertheless, the tremendous capacity for growth and differentiation of the lining epithelium of the vagina and uterus of the rodent deserves consideration in any attempt to explain the occurrence of epidermidization in the human.

It seems justifiable to draw the following general conclusions from personal observations and the findings which have been reported by many careful investigators. (1) The cells of the mucosa lining the vagina and uterus of the mouse and rat have the capacity of reacting to various stimuli and undergoing anatomic transformations as to shape, size, form, and tissue organization. (2) These changes may be accompanied by physiologic transformations, for example, a cell secreting mucus may assume a glycogenic function or become an inactive protective keratinized unit. (3) This capacity is an inherent property, but the mature cell itself does not undergo this change. (4) It is accomplished by the intervention of an active offspring which results from mitotic division of the existent parent.

SUMMARY

1. Epidermidization is a basic physiologic process by which the cylindrical epithelium of glands and surfaces of the cervix and endometrium is converted into stratified squamous epithelium. In contradistinction, epithelialization refers to growth of adjacent squamous epithelium over a surface denuded by trauma or inflammation and occurs normally in wound healing.

2. Epidermidization is fundamentally benign and must not be confused with carcinoma in situ nor with anaplastic changes involving the basal cells of squamous epithelium. However, it does occur in adenocarcinomas of both cervix and fundus uteri.

3. Epidermidization has been described at all ages from intrauterine life to old age.

4. A frequent occurrence in the normal cervix, epidermidization has been found most often in the cervix of the newborn, the cervix of the mother during pregnancy, chronic cervicitis, erosion of the cervix, mucous polypi of the cervix, hyperplasia of the endometrium, and endometrial polypi.

5. The exact cause for this change is not known, but experimental studies, as well as observations during pregnancy and accompanying certain endocrine dysfunctions, indicate that epidermidization in the uterus is influenced by hormonal, especially estrogenic, substances.

6. The steps by which epidermidization is brought about have been adequately studied in both human material and experimental animals. The first stage consists of the appearance of small cells (basal cells, infraepithelial cells, reserve cells) between the basement membrane and the overlying cylindrical epithelium. These cells have the inherent capacity of developing into either normal cylindrical epithelium or stratified squamous epithelium.

7. There are objections to accepting the concepts that these basal cells are (1) outgrowths from adjacent squamous epithelium, (2) remnants of pre-existing (fetal) squamous epithelium, (3) undifferentiated cellular rests of embryonic origin, or (4) a direct metaplasia of adult cells.

8. Epidermidization, or an apparently identical histologic picture, may be reproduced experimentally in the vagina and uterus of laboratory rodents. In them it results from proliferating units derived from normally existing cylindrical epithelium.

[1]Although not pertinent to the subject of this paper it seems proper at this point to mention the occurrence of tissue leucocytosis in the rodent vagina and uterus. In a great majority of instances of metaplasia, not only in the uterus but in other organs in both sexes, varying degrees of infiltration of the stroma and mucosa with leucocytes have been found. The subject has been discussed by several investigators, notably Burrows, but seems to have been overlooked by the gynecologic pathologist. Since a similar leucocytic infiltration is so often noted in the human cervix and uterus and it is generally ascribed to inflammation the question well deserves attention. It would not be surprising if the great incidence of "chronic cervicitis" with accompanying erosion is not always due to infection but to a hormonal change also evidenced by epidermidization.

9. These observations lend support to the theory that the basal cells concerned in epidermidization are derived by an indirect metaplastic process from normal or malignant cylindrical epithelium.

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FURTHER INVESTIGATIONS ON THE USE OF HEPARIN IN THE TREATMENT OF EXPERIMENTAL FROSTBITE

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RENEWED interest in the problem of local cold injury has become manifest in the past decade because of the large number of casualties from cold which occurred in World War II and the present Korean conflict. Of the many investigations on therapy those of Lange and collaborators (3, 6, 7, 9, 10) have been especially notable since they reported from a number of experiments that heparin either prevented or markedly reduced the incidence of gangrene after local cold injury. Fuhrman and Quintanilla and their associates, as well as the present authors (15), failed to lessen the incidence of gangrene in cold-injured rabbits treated with heparin.

Lange and associates (8) have strenuously objected to the investigations mentioned (in which failure of heparin was reported) on the grounds that insufficient amounts of heparin were used since blood coagulation times were not kept continuously above 30 minutes during the period of treatment.

We believe that only the use of animals in carefully controlled laboratory experiments can furnish the solution to this controversy.

This investigation was carried out to determine whether heparin therapy (3 days for muscle gangrene and 5 days for skin necrosis) would decrease either the incidence or the extent of gangrene in frozen rabbit legs when the blood coagulation time was continuously increased to 30 minutes or longer.

MATERIALS AND METHODS

Male albino rabbits weighing 2½ to 3½ kilograms were used in 13 separate experiments which were conducted from June to December 1952 comprising 466 rabbits (314 heparin-treated and 152 controls). A hind leg was depilated and exposed to an alcohol bath as described in another paper (15). We had previously determined the exposure conditions which are critical for muscle and skin survival (17). It was believed that these levels of exposure should be used since they result in injuries from which spontaneous recovery is not possible in the overwhelming majority of animals and still are not so severe as to preclude at least partial recovery as evidenced by the beneficial results obtained from rapid thawing (16). Exposures to a bath at −12 and −15 degrees C. for 30 minutes were used for the determination of muscle and skin necrosis, respectively. The extent of skin necrosis and areas of muscle necrosis were measured 1 and 2 weeks after exposure, respectively, as described in another paper (18). Two hundred and fifty-one animals were used to determine the extent of skin necrosis (177 treated and 74 controls) and 215 for the extent of muscle necrosis as well as the incidence of skin necrosis (137 treated and 78 controls).

The animals were anesthetized with pentothal sodium during exposure, and in all experiments the first dose of heparin was given immediately after the cold exposure.

Aqueous heparin (1,000 units per c.c.) injected intravenously was used in the first 4 experiments. Doses of 2 cubic centimeters were given at intervals which varied from 1 to 4 hours depending on the blood coagulation times which were maintained at or above 30 minutes continuously during the period of heparin administration. The very high death rate resulting from the large doses of intermittently administered aqueous heparin (53 of 62 animals died before the end of the 4 experiments) required to maintain the coagulation time at 30 minutes or greater forced us to change to a depot-type heparin. In the remaining 9 experiments heparin repository (20,000 units per c.c.) was used. To minimize errors in measuring small volumes of the prep-

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aration, the heparin was diluted 1 to 1 with placebo repository menstruum furnished by the manufacturer. One-fourth cubic centimeter of the diluted mixture (2,500 units) was injected every 8 hours in the thigh muscles of the unexposed leg in experiments 5 through 9. Later it was discovered that a satisfactory prolongation of the coagulation time could be obtained by the subcutaneous administration of 1.0 cubic centimeter of the diluted preparation (10,000 units) in the abdominal wall every 24 hours. An effort was made to use the minimum amount of heparin to produce the desired prolongation of the coagulation times so as to minimize the death rates.

In animals exposed to −12 degrees C. for 30 minutes for the determination of muscle necrosis heparin therapy was continued for only 72 hours since muscle necrosis is well developed by that time. Animals exposed to −15 degrees C. for 30 minutes for the determination of skin necrosis were treated for 5 days since some animals do not develop well demarcated areas of skin gangrene before this time.

All surviving animals were sacrificed at the end of the 1 or 2 week experimental periods, and any animal dying near the end of the period was used in the final evaluation. If 1 animal of a series died late and was used, all subsequent animals which succumbed were also evaluated regardless of the extent of tissue damage.

Except for heparin administration the control and experimental animals received the same care consisting of local application of sulfamylon ointment and a dressing which was changed daily. Water and a prepared rabbit food were allowed ad libitum.

Blood coagulation times were determined by the glass capillary tube method using venous blood as described later and were performed on each animal immediately before each injection of heparin, with the exception of the first.

In the first 4 experiments, in which aqueous heparin was used, 20 to 22 centimeter lengths of small caliber polyethylene tubing were inserted into the marginal vein of both ears of each rabbit so that the proximal tips were near the heart. One tube was used to inject heparin and the other to collect blood samples in the capillary tubes by gravity for coagulation determinations during the entire experimental period of either 1 or 2 weeks. With the use of repository heparin intramuscularly (experiments 5 through 9) only one ear was cannulated for the withdrawal of blood samples. Finally, when the repository heparin was administered subcutaneously (experiments 10 through 13) venous cannulization was not necessary since only 1 sample was required each 24 hours. In these the blood was withdrawn by means of a 22 gauge hypodermic needle fixed to the capillary glass tubing with soft paraffin as described by Pichotka and Reichel (19). The capillary tubes were coated internally with silicone in all experiments except the first 4.

In heparin-treated animals which died before the end of the experimental periods autopsies were made, and the anterior muscles of the exposed legs (tibialis anticus and extensor digitorum longus) were removed, examined for gross changes, fixed in formalin, and sectioned for histologic examination.

In animals which survived, macroscopic examination of the leg muscles was performed for evidence of gross gangrene.

It was not possible to obtain a sufficient number of live animals in any one experiment to draw valid conclusions. Therefore, all animals exposed to −12 degrees C. and used for evaluation were treated as a single group, as were those exposed to −15 degrees C. This manner of treatment is not ideal since we know that groups of animals subjected to the same conditions of exposure at different seasons of the year may not, for reasons not clear, develop the same degree of injury. However, since adequate control groups were included in each experiment, it was believed that the same variation would be reflected in both treated and untreated animals.

The chi-square and the Mann-Whitney rank order tests were used for the statistical analysis of the data (14).

RESULTS

The results of heparinization on the incidence and extent of muscle and skin gangrene are summarized in Tables I and II. Of 137

animals exposed to −12 degrees C. for 30 minutes and heparinized for 3 days, only 38 survived the experimental period of 2 weeks, and 3 lived sufficiently long to be evaluated. There was a significantly greater incidence of muscle necrosis in the heparinized animals ($P=0.03$ by the chi-square test). Also, the extent of necrosis of the leg muscles was significantly greater in the heparinized animals than in controls ($P=0.03$ by the Mann-Whitney test). Although the incidence of skin necrosis was somewhat less in the animals treated with heparin, analysis revealed that the difference was not significant ($P=0.5$ by the chi-square test).

Forty-six of 177 animals treated with heparin exposed to −15 degrees C. for 30 minutes were evaluated for the incidence of muscle and skin necrosis and the extent of skin gangrene. All heparinized and control animals developed muscle gangrene. The incidence of skin gangrene was practically the same in treated and control animals ($P=0.8$ by the chi-square test), whereas the extent of skin necrosis was greater in those heparinized but not significantly so ($P=0.46$ by the Mann-Whitney test). All 33 surviving heparinized animals showed extensive gangrene of the leg muscles at autopsy.

Blood coagulation times in the surviving animals exposed to −12 degrees C. for 30 minutes remained at or above 30 minutes during the 3 day treatment period. Coating the tubes with silicone resulted in considerable prolongation of the determined coagulation times after heparin administration. As a rule, the coagulation times were shortened considerably as we approached the end of the experimental period. Those animals which succumbed were found to have coagulation times greater than 30 minutes to the time of death.

The animals exposed to −15 degrees C. for 30 minutes which lived to the end of the experimental periods demonstrated a continuous blood coagulation time of 30 minutes or longer except in 3 animals. In 2 of these the clotting time dropped to 25 minutes on 1 occasion during the course of heparin therapy. The third showed clotting of the blood at 15 minutes on the last day of treatment. The latter animal was used in the calculation in that it showed a very good end result, developing only 0.13 square centimeter of skin necrosis, which is much below the average amount.

TABLE I.—EFFECT OF HEPARIN ON THE DEVELOPMENT OF MUSCLE NECROSIS (EXPOSURE AT −12 DEGREES C. FOR 30 MINUTES)

No. animals exposed	No. survived	No. with skin necrosis	No. with muscle necrosis	Muscle necrosis per cent
137 heparinized	38(3)*	7	41	20.1± 2.3
78 controls	69	17	61	15.5± 5.9

*No. in parentheses denotes animals which died sufficiently late in the experiment to have well demarcated areas of skin gangrene and were, therefore, used in the evaluation.

The microscopic observations made of the leg muscles in the heparinized animals which died prior to the end of the experimental periods are very important. Of 243 such animals 240 were studied, and without exception all showed acute muscle degeneration of the character described in another paper (18) (1 was discarded without autopsy and 2 showed gangrene of muscle on gross examination). Of these the muscle degeneration was severe in 226, moderate in 8, and mild in 6 animals.

The general condition and death rate of the heparinized animals showed differences when compared to the controls. As a rule the treated animals consumed lesser amounts of food and water than the controls during the experimental periods and showed little physical activity. Many never got on their feet and died within a few hours after treatment was begun. The average weight loss was significantly greater in the heparinized animals, both those exposed to −12 degrees and those exposed to −15 degrees C. In the former group the average weight loss was 277.6±31.8 grams (9.7±1.8 per cent) for the treated and 73.6± 21.8 grams (1.8±0.5 per cent) for the controls. The animals treated with heparin exposed to −15 degrees C. showed an average weight loss of 388.2±32.3 grams (12.2±1.1 per cent) compared to 195.3±19.8 grams (6.3±0.6 per cent) for the untreated controls. The difference in per cent weight loss in both groups is highly significant ($P=<0.001$ in the −12 degrees and $P=<0.001$ in the

TABLE II.—EFFECT OF HEPARIN ON THE DEVELOPMENT OF SKIN NECROSIS (EXPOSURE AT −15 DEGREES C. FOR 30 MINUTES)

No. animals exposed	No. Survived	No. with skin necrosis	No. with muscle necrosis	Skin necrosis sq. cm.
177 heparinized	33(13)*	38	46	23.0± 3.4
74 controls	49	41	49	17.6± 2.3

*No. in parentheses denotes animals which died sufficiently late in the experiment to have well demarcated areas of skin gangrene and were, therefore, used in the evaluation.

−15 degrees C. animals by the Mann-Whitney test).

The death rates in the treated and untreated animals showed considerable differences. Of 137 heparinized animals exposed to −12 degrees C., 99 died before the end of the experiments compared to 9 of 78 similarly exposed but untreated controls. The difference is highly significant ($P = <0.001$ by the chi-square test). The same situation prevailed in the animals exposed to −15 degrees C. One hundred and forty-four of 177 heparin-treated animals compared to 25 of 74 controls died before the end of the experimental periods. Again, the difference is very significant ($P = <0.001$ by the chi-square test).

The cause of death was not apparent in all heparinized animals although autopsies were performed (Table III). Internal hemorrhage sufficiently severe to be considered the cause of death was present in 52 animals, being abdominal in 21, intramuscular in 23, subcutaneous in 4, pulmonary in 7, and intestinal in 1. In 4 animals hemorrhage occurred in 2 locations. The abdominal hemorrhages were retroperitoneal (except for 1 which was into the lumen of the colon) and almost always in the vicinity of the left psoas major muscle which showed partial or complete rupture in most instances. In 191 animals not demonstrating hemorrhage no cause of death was found. These animals became gradually weaker, developed labored and rapid respiration, often had fever of 103 to 110 degrees F., and died with or without mild or moderate clonic contractions of the body musculature.

DISCUSSION

The results of our 13 experiments failed to demonstrate any benefit from heparin therapy either with regard to the incidence or the extent of skin and muscle necrosis. We arrived at a similar conclusion in previously reported experimental studies (15). However, we admitted in the latter paper that we were unable to prolong the blood coagulation time continuously for 30 minutes by using the heparin doses and injection intervals used by Lange and associates. After our own experience and those of others, it hardly seems worth while to discuss the possibility of prolonging continuously blood coagulation time for 30 minutes by injecting aqueous heparin intravenously every 12 hours in rabbits or other species of animals, and it is doubtful that injections every 6 hours will suffice for the purpose. We cannot adhere to the idea that the strain of rabbits, their size, method of determining clotting times, or feeding conditions can account for the great discrepancy in blood coagulation times between our animals and those used by Lange and associates. Shumacker and collaborators (22) experienced the same difficulties in this respect with rabbits as we did.

It is not clear why Lange and collaborators evaluated certain animals whose coagulation time dropped as low as 22 minutes, although they recommend in several papers that it be kept between 30 and 60 minutes.

The amount of heparin per kilogram of body weight required to maintain an elevated coagulation time appears to be considerably greater for rabbits than for other animals or man, and the amount necessary may vary considerably in individual rabbits. It is obvious from their general condition and from the death rate in our experiments that more heparin was required than was compatible with the well being of the animals. Hoelscher has demonstrated degenerative changes in the cells of the adrenal cortex in frostbitten rabbits treated with relatively large amounts of heparin. Certainly attempts should be made to use some other animal, although we felt obligated to use rabbits since they were employed by Lange and collaborators in the experiments which popularized this form of therapy.

Lange and associates (8) also took exception to the statistical analysis of the results

in our first heparin report (15). They state that our results revealed only 40 per cent (2 out of 5) of one series of animals developed complete necrosis of the leg, whereas complete gangrene occurred in 79 per cent (26 out of 33) of all surviving controls used in 3 separate experiments. Five animals are too few to be considered in percentages and it is misleading in this instance. Statistical analysis by Fisher's exact method for analysis of the fourfold table does not show a significant difference in the two results (P=0.10).

To draw sound conclusions from published results on the use of heparin in experimental frostbite one must critically analyze the experimental procedures used. A most important factor is the method used to produce a so-called standard injury. In several of the investigations of Lange and his associates (6–8) both the time of exposure and the temperature of the exposure bath to which the rabbits' legs were exposed were allowed to vary considerably. The exposures were made at temperatures of from −12 to −20 degrees or −30 degrees C. for from 30 to 45 minutes in 1 experiment and from 45 to 90 minutes in the other 2 experiments. Obviously, experimental results obtained under such conditions are of little or no value. It must be borne in mind that, other conditions being equal, the degree of injury is dependent on the product of the exposure temperature and time. A variation in this time intensity product will alter the final injury as is the case with other physical and chemical stimuli.

The reports of Lempke and Shumacker and of Shumacker and associates (22), on which Lange and associates lean so heavily for support, deserve some comment in this regard. In the latter investigation using rabbit legs, the bath temperature was allowed to vary from −20 to −40 degrees C. or from −12 to −20 degrees C. and, although the exposure time was kept constant for each experiment, a uniform reproducible injury could not be expected to result. We have shown that a difference of exposure temperature of only 3 degrees C. for a constant exposure time of 30 minutes in an alcohol bath results in a much different degree of cold injury to rabbit legs (17). Also, from the small number of animals used for each regimen of heparin therapy and the results obtained, it is not convincing that heparin was of value in reducing the incidence of gangrene in the experiments by Shumacker and associates (22). No tests for statistical significance are given, and coagulation times were not performed on the frozen heparin-treated animals but on unfrozen animals. It is doubtful that it can be assumed that the coagulation times in frozen and unfrozen animals would be comparable since in our experience larger doses of heparin are required as the gangrenous process progresses. This observation is in accordance with the findings of deTakats and of Brambel and Loker. The former found that blood coagulation was delayed following surgical operations, presumably because of the liberation of thrombokinase, and the latter observed increased prothrombin activity in phlebitis, postoperative surgical trauma, and during childbirth. In the investigation of Lempke and Shumacker (12) mice tails were frozen and heparin given at either 3 or 4 hour intervals for 72 hours. Again, blood coagulations

TABLE III.—DEATHS IN HEPARIN-TREATED ANIMALS

Experiment No.	No. of animals treated	No. of animals that died from unknown causes	No. of animals that died from hemorrhage	No. of animals that survived	No. of animals that died but used in evaluation	Total No. used for evaluation
1	8	3	4	1	0	1
2	16	14	2	0	0	0
3	18	5	10	3	2	5
4	20	13	4	3	0	3
5	21	13	2	6	1	7
6	24	6	8	10	0	10
7	23	14	4	5	4	9
8	25	15	5	5	1	6
9	33	29	2	2	3	5
10	30	24	1	5	2	7
11	30	13	2	15	0	15
12	33	22	2	9	2	11
13	33	20	6	7	1	8
Totals	314	191	52	71	16	87

Aqueous heparin administered intravenously in experiments 1, 2, 3, and 4.
Repository heparin administered intramuscularly in experiments 5, 6, 7, 8, and 9.
Repository heparin administered subcutaneously in experiments 10, 11, 12, and 13.

were not determined on the experimental animals but on nonfrozen heparinized mice. Although no tests for statistical significance are given, it would appear from their data that the best results were obtained from rapid thawing and rapid thawing plus etamon. The results from heparin injected every 4 hours do not appear to be better than in control animals, although the results from administration every 3 hours apparently favor heparin.

Even though the bath temperature, exposure time, and the depth to which an extremity is immersed are kept constant, one prominent uncontrolled factor prevents the production of a uniform injury in all animals. This factor is the varying ability different animals possess to defend the exposed parts from the cold and is the result of the animal's vascular heat-regulating mechanism. This problem necessitates the use of relatively large numbers of animals to be reasonably sure of obtaining valid results. In our experience about 4 of every 100 rabbit legs exposed to an alcohol bath at —12 degrees C. for 30 minutes escaped freezing of even the skin. In only 1 animal of some 2,500 similarly exposed to —15 degrees C. for 30 minutes was freezing completely avoided. This ability to ward off the injury is, of course, greater when the part is exposed to relatively still cold air in contrast to liquid since the former is a poor thermal conductor.

The most obvious way to avoid this problem in experimental studies would be to apply a tourniquet to the extremities during exposure. We have been reluctant to do this for fear that critics would be inclined to blame at least some of the resulting injury on the tourniquet-induced ischemia, although we know that 30 minutes of such induced ischemia by itself does not result in anatomic tissue changes.

It is this great variation of final injury in human cases exposed to very different conditions of cold exposure that makes evaluation of clinical reports so difficult. A typical example is the paper of Theis and collaborators who treated 14 of 30 cold-injured patients with anticoagulants and concluded that those treated with heparin and dicumarol fared much better than those not receiving this therapy. They admit that the exposure temperatures, duration of exposure, type of exposure, wind velocity, and general condition of the afflicted individuals were not the same and often could not be determined. Since all of these factors influence the degree of injury, it is not possible to divide such patients into two groups representing equivalent injuries. Any conclusions drawn, therefore, are little more than conjecture.

The degree of injury used by various investigators to test therapeutic responses needs comment. It has been usual to use conditions which result in the same degree of injury in all animals. Since gangrene, the most severe end result, is the only clear-cut criterion by which to measure the injury, a degree of exposure is generally used that will result in complete gangrene of the exposed part. In many instances such exposures have been more severe than required to produce such necrosis and, therefore, often result in injuries that preclude recovery. The ideal exposure would be one that produces an injury just beyond that from which spontaneous recovery is not possible for most of the animals.

We have described injuries less severe than those ending in gangrene (17). These lesser injuries vary from mild sensory changes to muscle paresis or paralysis and atrophy of muscle and skin. It is quite apparent that the sensory disturbances and muscle paresis or paralysis, which occur immediately after the cold exposure, are due to the direct action of cold on nerves (or end organs) or muscles and perhaps both. Since all the observed changes after cold exposure represent different degrees of injury which are consecutive, it seems reasonable that the more severe organic lesions, such as atrophy and gangrene, are produced in the same manner.

We are prepared to defend our use of heparin for only 3 days for determination of its effect on the production of muscle necrosis. In many hundred cold-injured animals we have demonstrated that muscle degeneration begins within a few minutes after exposure, within 48 hours macrophages can be observed phagocytosing dead muscle, and within 72 hours the muscle gangrene is visible macro-

scopically (13). We are quite confident that the fate of the skin is also determined within the same period of time, although more time is generally required for complete demarcation. In not a few instances the necrosis of skin is sufficiently well demarcated to measure on the fourth day.

We have also learned that with cold-injured rabbit legs one cannot conclude that a leg has escaped gangrene because the skin remains viable. Many legs with completely viable skin show extensive gangrene of the underlying muscles.

It is reasonable to expect any beneficial treatment to give good results which are reproducible in the hands of most investigators —just as rapid thawing has proved of benefit by all that have reported on it. In our experience rapid thawing almost always prevented skin gangrene in rabbit legs following cold exposures which have proved to be critical for skin survival. It seems to us that, if heparin is a beneficial therapeutic agent, it should become apparent at these levels of injury which were the ones used in this investigation.

The use of heparin in cold injuries is based on the assumption that tissue death is secondary to vascular thrombosis. Our observations are not in agreement with this hypothesis. Thrombosis has not been observed earlier than 24 hours and is seen only in areas already necrotic. We have concluded from this observation that the thrombosis in cold injuries is a secondary and protective mechanism, just as it is in other destructive injuries (for example, tuberculous necrosis of the lung).

Although the results in a single case are inconclusive, it is interesting that the patient reported by Laufman lost both legs below the knee as well as all fingers except a thumb, even though therapeutic levels of anticoagulative therapy (heparin, dicumarol, and 2-phenylindanedione) were maintained for 22 days.

In 2 recent publications by Lange and associates (8) and Shumacker and Lempke (21), statements were made that we had been able to save 60 per cent of cold-injured tissue that would otherwise have become necrotic by using anticoagulants (heparin and dicumarol). These statements were based on a personal letter written by the senior author to Lange in 1947 just as we were beginning our cold experiments. Since they intimate that we have suppressed data which would favor anticoagulative therapy, we believe that an explanation is in order. Our first attempts to produce a standard injury were made by holding a 1 inch cube of carbon dioxide ice in a large hemostat and applying it manually to the shaved abdominal skin of rabbits for a given period of time. At the end of a week the necrotic skin was palpated and measured in diameter and thickness with a ruler as best we could. The first 5 animals treated with heparin and dicumarol when compared with 5 similarly exposed but untreated controls showed what we estimated to be 60 per cent less necrosis. Our optimism was cut short, however, when we subsequently discovered that the degree of cold injury so obtained was not a reproducible one, apparently because of differences in pressure while applying the cube of ice, differences in angle of application, and perhaps for other reasons. We, therefore, changed to the immersion method of producing cold injuries which has proved much more satisfactory. Since the results of those preliminary experiments were not published, we did not believe that retraction of the statements made in a personal letter was necessary.

SUMMARY AND CONCLUSIONS

The extent of muscle and skin necrosis was determined in 87 (71 survivors and 16 which lived sufficiently long to be used) of 311 heparinized rabbits following exposure of a hind leg to cold alcohol at either −12 or −15 degrees C. for 30 minutes in 13 separate experiments. The results were compared to those from 118 similarly exposed but non-heparinized animals. The incidence and extent of gangrene were not less in heparinized animals, even though blood coagulation times were kept at or above 30 minutes during the treatment period.

The death rate in the heparin-treated animals was significantly greater than in the control groups.

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INTRAMEDULLARY NAILING OF FRACTURES OF THE SHAFT OF LONG BONES

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INTRAMEDULLARY nailing of shaft fractures of the long bones was introduced by Küntscher in 1940. The method has been tried especially by German and Scandinavian surgeons. The reported results have been varying. The field of indication and technical details of the method are still under discussion.

The present paper is an evaluation of the results of this treatment and may serve to elucidate some problems in the application of the method. At Drammen Hospital 80 patients were treated by intramedullary nailing during the period 1942 to 1951. The femur was the site of the fracture in 24 patients treated, 10 of these fractures being short oblique and 14 transverse; the tibia, in 20 patients with 10 short oblique, 8 transverse, and 2 compound; the humerus, in 10 with 5 short oblique, 4 transverse, and 1 pseudarthrosis; the forearm, in 26 patients with 12 short oblique, 10 transverse, 2 compound, and 2 pseudarthroses, making a total of 37 short oblique fractures, 36 transverse, 4 compound, and 3 pseudarthroses. Follow-up studies including x-ray and physical examination were made in all cases. The period of observation varied from 1 to 6 years, with an average of 2 years and 3 months.

INDICATIONS

Encouraged by his first results, Küntscher recommended intramedullary nailing for all kinds of shaft fractures, in children as well as in elderly patients. Later experience, however, made some limitation of these indications necessary, though new types of fractures such as the following seemed to be suitable for this method: various types of pseudarthrosis and war fractures as well as, in some cases, fractures of the clavicle, the small bones, and spontaneous fractures. We have used intramedullary nailing mainly in instances of diaphyseal fractures of long bones when satisfactory reduction or stable fixation of the fragments were not obtained by other methods. In certain cases it was also used when it was especially desirable to shorten the stay in the hospital, and when other methods of treatment were impracticable, for example, in cases of the insane.

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SURGICAL TECHNIQUE

Küntscher claimed that one of the advantages of his method was that *closed* reduction could be followed by insertion of the nail at a distant site, from which it might be driven down the medullary cavity through the fracture.

We have found this "nailing per distance" inadequate, as satisfactory closed reduction cannot always be achieved, even with the most efficient roentgenologic service. We prefer exposure and open reduction before insertion of the nail, as recommended by Palmer in 1944. This procedure, in general, involves less surgical trauma of the tissues than lengthy, closed manipulation of the fragments.

In the present series, spinal anesthesia was used in lower limb fractures and general anesthesia in fractures of the arms. The nails most commonly used were those with gutter-shaped cross-sections and with edges curving inward (Fig. 1). The choice of the nail may be of some difficulty and a selection of them should always be available during the operation.

From the point of view of technique, even where the correct nail has been employed, additional fixation is recommended. Apparently, the V shaped Küntscher nail offers the best fixation as compared with other pins for intramedullary use. But the theory of Küntscher that the fixation by this nail was absolute has failed. Therefore, we always use

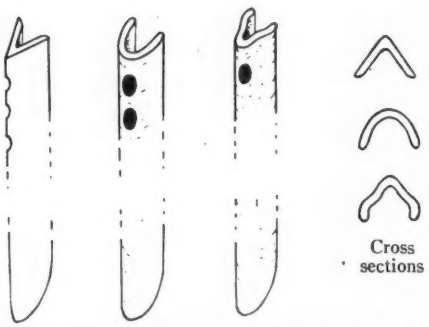

Fig. 1. Different types of nails (the V shaped most commonly used).

a plaster cast postoperatively in fractures of the leg and forearm and occasionally in fractures of the femur too. Operative technique at Drammen Hospital deviates in some respects from that of Küntscher and the following points from our experience are worth stressing:

Femur. The patient is placed on his uninjured side with his opposite hip slightly flexed. The fracture is exposed and through it a guide pin is inserted proximally into the medullary cavity, penetrating the cortical bone in the trochanteric region. A small incision is made in the skin at the point where the guide pin is felt, and the nail is then driven down the guide (Fig. 2). Difficulty in selecting the correct site for the insertion of the nail is thus obviated.

Tibia. The nail is inserted as obliquely as possible from the medial aspect of the tibial tubercle through a chiseled hole in the cortical bone. In driving in the nail, it bends a little, which may cause slight posterior and lateral angulation at the fracture site. The alignment, however, can easily be corrected when the immobilizing plaster cast is applied or when the cast is renewed (Fig. 3). If the drilled canal is not made sufficiently oblique, the nail may bend too much, causing diastasis of the fragments, and delayed union may occur.

Humerus. As a rule, nailing has been carried out at the greatest distance from the fracture, but, if possible, we prefer insertion of the nail through the lower end of the bone, instead of through the great tuberosity (Fig. 4). Often too, thin nails are chosen, the fact that the medullary cavity has almost the same width throughout the upper 2/3 of the bone being ignored. Too thick nails, on the other hand, may cause damage to the bone or they may become entirely impacted. If the nail meets great resistance it should at once be replaced by a smaller one.

Radius. As in fractures of the humerus, we prefer to insert the nail proximally (Fig. 5), but if the distal fragment is less than about 8 to 10 centimeters, splintering of the bone may occur. The nail should in these cases be introduced through a short incision at the upper end of the bone.

Ulna. To some extent the same applies to this bone as to the femur, the nail is driven down a guide wire inserted proximally in the medullary cavity; but we often make a primary insertion through the olecranon process (Fig. 5).

It is very important to avoid diastasis at the site of the fracture! As a rule, this may be achieved when the last fragment is kept firm during the insertion. Four to 6 months after the primary operation the nails are usually removed with an extractor especially made for that purpose.

RESULTS

In the clinical material mentioned, the end-results of the intramedullary nailing vary a little, apparently depending on the type and site of the fractures.

Fractures of the femur. Osteotraction with or without plaster cast immobilization was tried as a usual procedure in 20 cases. Intramedullary nailing was then performed between the second and fifth weeks after admission, as the primary treatment did not appear successful. In 8 patients oblique fractures beneath the minor trochanter were found, 4 of which were nailed the day of admission. The tendency of dislocation of the upper fragment because of the iliopsoas muscles makes these fractures unsuitable for treatment by traction and for fixation by stainless steel wire or plating. According to our experience, nailing should be the treatment of choice in subtrochanteric adduction fractures. In 3

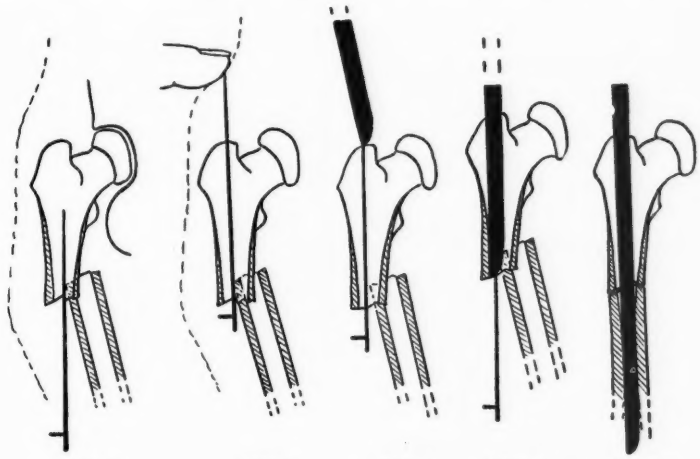

Fig. 2. Intramedullary nailing of fractures of the femur (upper half of the shaft).

cases reduction was accomplished without surgical exposure prior to nailing, while open reduction was necessary in 21 cases. Postoperatively, the limb was immobilized in a Braun or Thomas splint in 14 cases. In 5 cases the leg was supported by pillows, and in 5 cases adequate fixation was not obtained with the nail alone, therefore, an immobilizing plaster cast was applied. Active muscular exercise was usually started a few days after the operation.

Excellent results were obtained in 16 of 24 cases, with perfect alignment and solid union occurring within a period of 3 to 4 months. Satisfactory functional results were obtained in 4 of the remaining 8 cases, although slight posterior angulation occurred in 3 of them. X-ray examination showed that nails which were too small had been used in these cases so that adequate fixation of the lower fragment had not been secured. Furthermore, 7 of the 8 cases mentioned were immobilized in a Braun splint which is less suitable than a Thomas splint besides its inconvenience in the general care of the patient. Poor results were obtained in 4 cases (Table I). The average number of days spent in the hospital after intramedullary nailing of fractures of the femur was 66 days in 22 cases during the period 1942 to 1951, as compared with 108 days in 16 cases covering the years 1935 to 1945 when traction and/or manual reduction plus plaster cast was used, and with 115 days in 24 cases from 1935 to 1945 when the treat-

TABLE I.—POOR RESULTS OF MEDULLARY NAILING IN FRACTURES OF THE FEMUR (OBTAINED IN 4 OF 24 CASES)

No.	Sex Age, years	Type of fracture	Treatment	Final results and remarks
1	M 63	Short oblique (left femur)	5th day, open red. + nail	Limps, 5 cm. shortening. Free movement at hip joint. X-ray: bony union, heavy callus formation. 4 months of work
2	M 76	Transverse (left femur)	2nd day, closed red. + nail	Senile dementia. Fracture of the nail 20 cm. above the knee. 6 cm. shortening. Walks badly with crutches. Unable to work
3	F 62	Short oblique (left femur)	4th day, open red. + nail	Persistent infection 1½ years after the injury. Repeated incisions, osteotomies, and sequestrectomies. Chemotherapy. Is still under treatment
4	M 22	Transverse (right femur)	2nd day, open red. + nail	Bending of the nail, due to walking on the nailed limb 14 days after the operation. Correction of the alignment, but new bending of the nail 1 month later resulted in pseudarthrosis. Did not return for a new arranged osteosynthesis

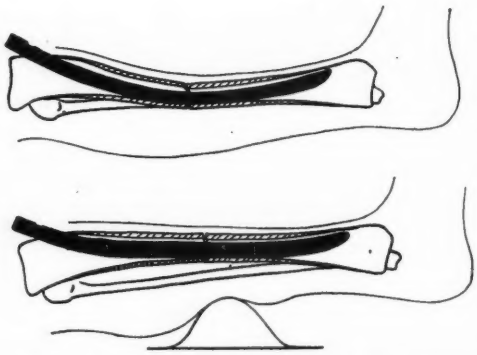

Fig. 3. Fracture of the tibia, treated by intramedullary nailing: above, posterior angulation at the site of the fracture; below, after correction of the alignment.

ment was fixation by plating (Cases 3 and 4, Table I, not included). Series for comparison were obtained by a study of 180 patients treated for fractures of the femur at our hospital during the period 1935 to 1945 (reviewed by Dr. H. S. Nissen-Lie). In 40 of these 180 cases (16 treated with plaster cast and 24 with plating) medullary nailing might have been profitable. Patients below the age of 15 years were excluded in both series of cases. The number of cases constituting each of the three groups is small, but the difference in early mobilization with medullary nailing is too great to be explained as being due to chance. With the exception of Cases 2, 3, and 4 (Table I), the period of incapacity for work was remarkably short following intramedullary nailing. One patient was disabled for 9 months. In the remaining 20 cases inability to work varied from 3 to 6 months.

Fractures of the tibia. At our hospital oblique fractures of the tibial shaft usually are treated by fixation by Parham's band. In most cases of transverse or *short* oblique fractures both traction and manual reduction, or either one separately, as well as plaster cast immobilization are used. In 16 cases, satisfactory apposition was not obtained by these methods, and medullary nailing was then performed within 2 weeks after the injury. In 4 cases of transverse fractures medullary nailing was used as a primary procedure.

Immobilizing plaster casts were applied in all cases. The patients could thus be sent home earlier than would otherwise have been possible. Later they were readmitted for extraction of the nail or kept under observation in the outpatient department.

TABLE II.—POOR RESULTS OF MEDULLARY NAILING IN FRACTURES OF THE FOREARM (OBTAINED IN 10 OF 26 CASES)

No.	Sex Age, years	Fracture of:	Treatment	Results and remarks
1	M 51	Radius	Open red. + nailing	Prolonged suppuration. After extraction of the nail and later sequestrectomies: satisfactory *function*, but x-rays suggest pseudarthrosis
2	F 20	Radius (and ulna)	Closed red. + nailing (Kirschner wire)	Poor alignment. Severe posterior angulatuin. Flexion and extension at elbow limited. Pronation and supination nil. Weakness of elbow + wrist
3	M 18	Radius	Open red. + nailing	Excellent *function*, but x-rays show fracture of the nail and suggest pseudarthrosis (hardworking farmer)
4	M 18	Ulna (and radius)	Open red. + nailing	Slight limitation of movement at elbow and weakness. X-ray: good alignment
5	M 55	Ulna (comminut.)	Open red. + nailing (+ excision of the head of radius)	Considerable limitation of elbow movement and weakness. Unsatisfactory alignment on x-ray
6	F 64	Ulna (and head of radius)		
7	M 23	Radius (complicated)	Open reduction + nailing	Slight weakness and limitation of movement at elbow. Unsatisfactory alignment on x-ray
8	M 54	Radius (complicated) + ulna		
9	F 61	Radius (comminut.)		
10	M 30	Radius (and ulna)		

The follow-up examination showed perfect anatomical and functional results in 15 cases (compound fractures in 3 cases, closed in 12). In 2 cases satisfactory alignment was obtained, but some limitation of movements of the knee joint persisted. In another 2 cases, the result was varus deformity and slight posterior angulation with limitation of dorsiflexion at the ankle joint, and discomfort in this joint on walking. (One of them, a 27 year old man, had also sustained a fracture of the neck of the left femur, which was nailed according to the method of Smith-Petersen.) In 1 case the operative technique failed, great diastasis of the fragments and pseudarthrosis occurring as a consequence. A new osteosynthesis was necessary. Infection did not occur despite open reduction of the fractures in 17 of the 20 cases. The stay in the hospital, including readmission, was remarkably short. The average number of days spent in the hospital after intramedullary nailing of the fractures of the tibia was 24 in 18 cases for the period 1942 to 1951, as compared with 40 days in 72 cases covering the years 1942 to 1949, when traction and/or manual reduction plus plaster cast was used and with 38 days (collected by Dr. Benjamin Wegener) in 75 cases from 1938 to 1947, when the treatment was fixation by Parham's band. (The 2 last patients, mentioned previously, are not included.)

On the other hand, there is little evidence to indicate that medullary nailing of tibial fractures, as compared with other procedures, shortens appreciably the convalescent period. In the present series it varied from 2½ to 11 months with an average of 4½ months. Furthermore, the rate of union of oblique fractures differs from that in transverse fractures. Finally, the nature of the patient's work is an important factor. A sedentary worker may resume his employment wearing a plaster cast at a much earlier date than a manual laborer.

Fractures of the humerus. Medullary nailing was done in 10 cases. In 8 cases of recent fractures, results are described as satisfactory and in 1 case of pseudarthrosis an excellent result was obtained. Open reduction was carried out 3 times. In 1, infection occurred, resulting in pseudarthrosis in a 35 year old patient. A new osteosynthesis was then performed.

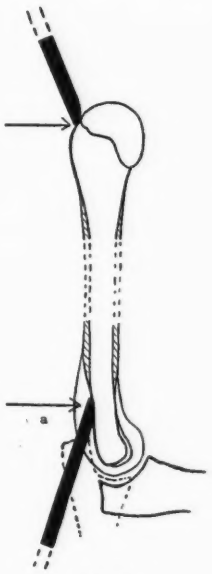

Fig. 4.

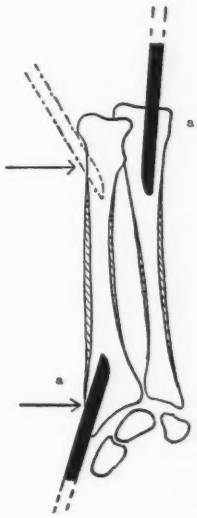

Fig. 5.

Figs. 4 and 5. *a*, Insertion of the nail at lower end of the bone is preferred.

A typical feature of most of these cases was heavy callus formation with fair alignment only, obtained in the majority. Imperfect alignment in 3 cases was probably due to the use of nails which were too thin and too short, giving poor fixation of the fragments and inadequate immobilization. The duration of inability to work varied according to the patient's occupation. It did not seem to be shorter than that following the use of other methods of treatment. The same applies to the period of hospitalization. However, definite conclusions based on so few observations cannot be drawn on this point.

Fractures of the forearm. Included in this group were 4 cases in which a Kirschner wire was used instead of a Küntscher nail. The principles of technique were otherwise the same as in medullary nailing.

Nailing was generally carried out immediately after admission in a comparatively large number of patients (9 cases), while other

methods were tried first in the remaining ones. An immobilizing plaster cast was applied in all cases. Open reduction was performed in 18 cases. Infection at the site of the fracture occurred in 1 of these. It involved a prolongation of the hospital stay. Solid union, however, occurred within 12 months. Satisfactory results, including perfect alignment and complete recovery of function, were obtained in 4 cases of fracture of the ulna, in 9 cases of fracture of the radius, and in 3 cases of pseudarthrosis of the radius. Heavy callus formation occurred in all cases. The less favorable and poor results obtained in the remaining 10 cases are listed in Table II.

Considering the group as a whole, medullary nailing was not entirely successful in fractures of the forearm. There were several reasons for this. A study of the roentgenograms in those cases left with more or less imperfect alignment indicates that too much reliance had been placed on the immobilizing effect of the nail. The cast was removed too soon or replaced by a shorter one, thus not giving adequate immobilization (for example, in a cast extending from the elbow to the metacarpophalangeal joints). Nails which were too short were used in 3 cases. Comminuted or multiple fractures, or crushing fractures of the elbow joint were usually the cause of residual disability at this joint (Table II). The head of the radius was excised in some of these cases.

The period of hospitalization is of less importance in these cases. The patient can usually be discharged after 1 or 2 weeks to be kept under observation in the outpatient department at regular intervals.

The duration of inability to work varied greatly, averaging 11 weeks. In view of the fact that most fractures of the forearm in which medullary nailing was used were of the more serious type, the results may be considered satisfactory.

CONCLUSIONS

In the present series of 80 cases intramedullary nailing has proved very successful in fractures of the femur and of the tibia while less satisfactory results were obtained in fractures of the forearm.

The number of factures of the humerus is too small to allow final conclusions, but, with 1 exception, good results were obtained in the few cases reported.

Infection at the site of the fracture occurred in 3 cases, in 2 instances it probably must be attributed to the method employed.

Open reduction is considered to increase the risk of infection somewhat, but this is outweighed by the other advantages of intramedullary nailing. A rapid open reduction probably involves less surgical damage of the tissues than a lengthy, closed manipulation of the fragments.

The stay in the hospital following medullary nailing of fractures of the femur and the tibia was remarkably short as compared with that following the use of other methods.

The usual methods of treatment should be tried before medullary nailing in simple diaphyseal fractures, at any rate in those of the tibia, humerus, and forearm. However, in the event of poor alignment or secondary displacement, medullary nailing should always be resorted to, preferably within 1 or 2 weeks after the injury.

Finally, there are certain types of fractures, especially of the femur, in which medullary nailing has been found empirically to be the method of choice.

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AN EXPERIMENTAL AND CLINICAL EVALUATION OF SURGICAL SUTURE MATERIALS

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MANY factors have to be considered when complications occur in postoperative wounds. The majority of papers on wound complications deal with disruption of abdominal wounds, which is perhaps reasonable as this is the most dangerous and dramatic occurrence, although not very frequent in Danish surgical clinics. Several excellent reviews of this subject have been written.

On the other hand, the more trivial wound complications are seldom mentioned in the literature. They comprise local hematomas, seromas, wound infection, delayed healing, incisional hernias, ugly scars, extrusion of suture knots or persistent sinuses, and, possibly also, intraperitoneal adhesions. Very often one of these complications prevents the attainment of healing per primam, the aim of every conscientious surgeon. As a matter of fact, the etiologic factors in the latter group do not differ essentially from the factors which cause wound disruption.

Most authors are agreed that wound complications occasionally can be attributed to suture materials and suture technique. In order to estimate their importance the following investigations have been carried out: (1) In experimental wounds in animals, the histologic reactions around various suture materials have been examined daily during the healing period and compared under identical conditions. (2) At the same time the function of the sutures was investigated. (3) Groups of patients whose wounds had been closed by known suture materials were followed up. The eventual early or late wound complications were examined, and suture materials or suture technique were taken into consideration as a causative factor on the basis of the results of the experiments that were performed in animals.

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ESSENTIALS OF BURIED ABDOMINAL SUTURES

One must realize that the demands made upon a suture are not the same in all tissues. If, for instance, a severed nerve has to be sutured the tensile strength of the suture is of slight importance, whereas the tissue reaction produced by the suture material, and especially the amount of scar formation, may influence conduction in the nerve bundles. In the closure of a fascial wound, on the contrary, the tensile strength of the thread and the stability of the knot are all important, and a quickly established and solid scar is desirable, whereas prolonged exudation will diminish the holding power of the fascial wound.

The present investigations deal with closure of clean abdominal wounds, and the demands made on buried abdominal sutures can be briefly summarized as follows: A suture material is required which does not produce tissue reactions that considerably weaken the holding power of the wound, and which is able to maintain an adequate tensile strength of the thread and to make certain that the knot does not slip during the 10 to 14 day period until the wound has regained sufficient strength. It must be sterile and without electrolytic effect; otherwise harmful tissue exudation is produced. It must be pliable and of uniform gauge, as thin as is compatible with security, in order to avoid damage of the tissue and insecure knots. It would be preferable that the suture not be roentgen-visible, and that overlooked cut ends would not migrate in the tissues or puncture the gloves. The suture must not produce pricking sensations in the scar, lesions of the intestines, or intraperitoneal adhesions. If the suture material is absorbed after it has fulfilled its function it is an advantage, but it is by no means absolutely necessary. Sterilization of the thread should be easy and effective, and its manufacture preferably simple and at a rather low cost.

Fig. 1. Fascial incision on one side of which is seen the reaction produced by a triangular curved needle for a thread of 0.40 millimeter gauge; 10 days postoperatively. ×24.

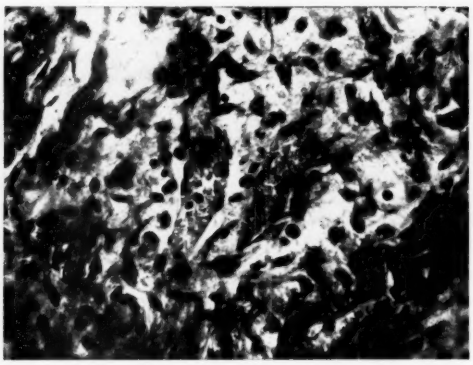

Fig. 2. Detail from Figure 1 with much higher magnification showing histiocytes, fibroblasts, and new capillary buds. ×202.

SKIN CLOSURE

For closure of the skin, only noncapillary materials should be used (and with very few exceptions only nonabsorbable materials) in order to avoid stitch abscesses, as it is impossible to disinfect the skin around the wound effectively for a sufficiently long time. Thin threads inserted with fine needles are preferable so that the damage of the skin will be minimal, but the sutures must be of adequate strength to secure exact cohesion of the wound edges which is all important to the final cosmetic result.

At the present time an ideal suture material does not exist which can be used for all purposes. This work aims at demonstrating the relative merits of various suture materials when used for closure of ordinary operative wounds in general surgery.

Fig. 3. Fascial incision on one side of which is seen the reaction produced by the strangulation trauma of tying a knot. The suture had been removed immediately afterward; 16 days postoperatively. ×24.

HISTOLOGIC REACTIONS AROUND SUTURES

These investigations are based on an examination of about 5,100 microscopic sections from 850 excisions of tissue around sutures inserted in 52 rabbits, 7 pigs, 5 rats, and 1 human volunteer. The usual preparation technique was used, with fixation of the excised tissue in formalin and staining of the paraffined slices with hematoxylin-eosin and the van Gieson-Hansen staining method.

Tissue reactions due to trauma. In order to estimate the histologic reactions produced around suture materials in wounds it was found necessary to study first the reactions caused by the mechanical trauma resulting from insertion of the sutures.

In a series of incision wounds in the obliquus externus fascia in rabbits, these reactions were examined on the fifth, tenth, fifteenth, and twentieth postoperative days in 4 sections of every wound, demarcated by nylon sutures. Section 1 comprised the linear fascial incision (the knife trauma). Through section 2 a curved triangular needle with eye was passed on both sides of the fascial incision. In section 3 the same needle was passed threaded with a suture of 0.40 millimeter gauge, and in section 4 the suture was temporarily tied with a triple

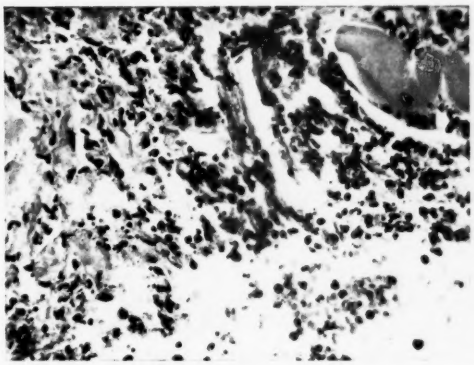

Fig. 4. Cellular reactions around a small bit of wood inserted in fascia; 5 days postoperatively. Exudation predominant. ×262.

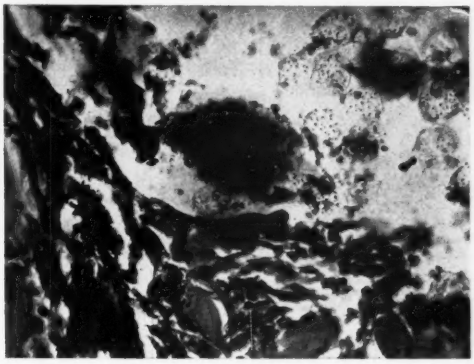

Fig. 5. Cellular reactions around a knot of multifilament nylon inserted in fascia; 5 days postoperatively. Fibroplasia predominant. ×262.

knot and removed immediately afterward so that the fascial tissue was exposed to the strangulation trauma of a tied suture.

On microscopic examination it was found that even minimum trauma, such as the prick of a needle, produced very distinct local reactions, a typical aseptic inflammation with slight exudation for about 5 days postoperatively followed by proliferation and cicatrization which was complete after 10 to 15 days (Figs. 1 and 2). The scar was still visible after 20 days.

The compression trauma caused by tying the knot produced a considerably increased zone of tissue reaction, and exudation was somewhat prolonged but fibroplasia was predominant on the tenth postoperative day; the scar occupied a distinctly wider area (about twice as wide) than after the needle prick (Fig. 3). These purely mechanically produced tissue reactions must not be disregarded in the histologic examination of suture materials. At the same time the necessity of gentle handling of the tissues is clearly demonstrated by this experiment.

Foreign body reactions. When sterile suture materials are inserted in musculofascial tissue the aseptic inflammatory reactions produced do not, in principle, differ from the reactions around other sorts of foreign bodies.

In rabbits, small bits of wood and glass of the same size, sterilized by autoclaving, and tied sutures of plain catgut and multifilament nylon were placed in fascial incision wounds. The various foreign bodies were excised together with the surrounding tissue for microscopic examination on the fifth, tenth, fifteenth, and twentieth days after operation. Around glass and nylon were found very few leucocytes, and no edema and fibrin on the fifth day, whereas exudation was marked around wood and plain catgut (Figs. 4 and 5). On the other hand, cicatrization seemed to be of relatively wider extent on the fifteenth day around glass and nylon than around wood and plain catgut (Figs. 6 and 7). The determining factors are probably the size and the molecular structure (the "fiber orientation") of the foreign body.

General factors in microscopy of sutures. A complete microscopic examination of buried sutures should be directed toward the following: (a) the absorption degree of the suture, (b) the zone of tissue reaction, (c) the degree of exudation, fibroplasia, and cicatrization respectively.

a. The author has found it adequate to classify absorption of sutures into six degrees: 0, no alteration of the suture, 1, superficial indentations caused by inflammatory cells, 2, deeper invasion of the suture, 3, fragmentation, 4, only small particles left, and 5, no traces of the suture. If the microscopic findings are co-ordinated with the function tests to be described later it is found that the tensile strength of a suture with absorption degree 0

Fig. 6. Tissue reactions around a small bit of glass inserted in fascia; 15 days postoperatively. Wide reaction zone with marked cicatrization. ×24.

is not affected; with absorption degree 1 it is only slightly decreased, whereas a suture with absorption degree 2, as a rule, will break when a traction of less than 2 kilograms is exerted upon it. With absorption degree 3 the suture has completely lost its continuity.

b. During the period of exudation and fibroplasia the extent of the reaction zone around a suture material is of decisive importance to the holding power of the tissue inside and around the suture loop. If the reaction zone is narrow there will still be undamaged tissue left on both sides of the incision. If, on the contrary, the reaction zone is wide the result may be that all the tissue inside and around the suture loop has become involved so that it is unable to resist traction on the suture.

Fig. 7. Tissue reactions around a small bit of wood inserted in fascia; 15 days postoperatively. Moderate reaction zone with slight cicatrization. ×24.

c. If the foreign body reaction is predominantly exudative the tissue in a few days becomes considerably weakened. As fibroplasia develops, its tensile strength is gradually increased, and the scar tissue possesses a holding power almost similar to that of the undamaged tissue.

Special factors in microscopy of sutures. The influence of the following special factors was investigated: (a) the species of the animal under experiment; (b) which section of the suture was examined, knotted or free end of the thread; (c) in which tissue layer was the suture inserted; (d) on which postoperative day the examination took place; and (e) the gauge of the suture.

a. In a series of experiments monofilament nylon and 3 different types of catgut were inserted in fascial wounds in rats, rabbits, and pigs, and the sutures with the surrounding tissue were excised on the third, sixth, twelfth, and twenty-eighth days postoperatively. The histologic reactions were found to be characteristic of each individual suture material, independent of the species of animal. In rabbits, however, both exudation and proliferation reached their maximum a few days later than in rats and pigs, and accordingly catgut absorption was a few days delayed in the former animals. These results were confirmed by simultaneous experiments on a rabbit and a human volunteer, in both of which 3 different suture materials were inserted into 6 fascial wounds; the sutures with the surrounding tissue were excised for microscopic examination 1, 2, 3, 5, 7, and 9 days postoperatively. The histologic findings were almost similar in rabbit and man, but catgut absorption was somewhat quicker in the latter. With this reservation rabbits seem to be suitable laboratory animals for suture research. Pigs are too expensive for use in routine investigations, and rats are too small.

b. In experiments on rats and rabbits in which 3 different types of catgut were inserted subfascially, on the right hindleg as untied threads and on the left hindleg as tied knots, a considerably slower rate of absorption was found with the tied sutures. This is hardly due

to the larger amount of catgut within the knots; other investigators have demonstrated that thick threads of catgut are absorbed as fast as, or sometimes even quicker than, thin threads. It seems more probable that the fibers of the catgut are brought into more intimate contact when a knot is tied so that cellular invasion is made more difficult; possibly the tying of a knot causes alterations in the nature of the foreign body as a result of higher degree of fiber orientation. This explains the reason that it is possible to demonstrate even within the same suture a much more marked cellular invasion of the free ends of the thread than in the knot and the adjacent parts of the suture (Fig. 8). In microscopic examinations of tied catgut sutures, therefore, as far as possible the same parts of the suture should be selected.

c. In 4 pigs identical suture materials were placed in the peritoneum, muscle, fascia, and the subcutaneous layer, and the microscopic reactions were examined 8, 16, 32, and 70 days postoperatively. With each individual suture material both absorption degree and reaction zone, as well as the cellular reactions, were practically the same in all the deep layers of the abdomen. These results do not agree with the findings of other authors who claim that the reactions around sutures in fascia are less distinct and absorption more retarded than for instance in muscle. Although the tensile strength of fresh fascia is extraordinary great fascia is by no means a tough covering which resists any brusque handling by the surgeon without producing tissue reactions. It is a most vital tissue layer in which gentle handling is just as necessary as in muscle or in the peritoneum.

d. It is of decisive importance on which day after operation the inserted sutures are examined. In a large number of rabbits the reactions around different suture materials were studied from day to day during the healing period, and in some animals the late reactions —after 30, 50, and 70 days—were also observed. It was found adequate to concentrate upon the tissue reactions on the fourth day when a maximum of exudation is found in the normal wound and the holding power of the tissue is at a minimum; on the eighth day when fibroplasia is normally predominant and the wound possesses a considerable tensile strength; and on the sixteenth day when a solid collagenous scar is usually formed and the tissue has practically regained its original holding power. These normal tissue reactions around the incision wounds were found to be more or less influenced by the various suture materials, especially with regard to the production of prolonged exudation and delayed fibroplasia.

Fig. 8. Section from parts of the same plain catgut suture; 14 days postoperatively. *a*, From the knot: slight absorption still present. *b*, From the free end of the thread: almost complete absorption. Fascial tissue. ×24.

e. As expected the size of the suture material is of essential consequence to the tissue reactions. The thicker the gauge the more widespread damage with tissue necrosis and exudation will be caused. This becomes especially marked if the suture material causes a specific exudation because of its foreign body

Fig. 9. Distinct peritoneal adhesions between an intestinal loop and 4 plain catgut sutures in the peritoneal incision wound. The other sutures indicated are of non-absorbable materials. From a pig; 8 days postoperatively.

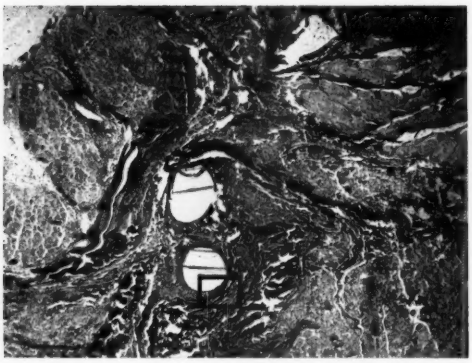

Fig. 10. Tissue reactions around monofilament nylon suture in fascia; 16 days postoperatively. Small reaction zone, no exudation. ×24.

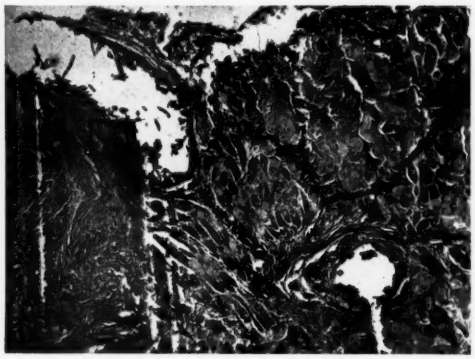

Fig. 12. Tissue reactions around black silk suture in fascia; 16 days postoperatively. Small reaction zone, no exudation. ×24.

nature, as for instance, plain catgut. A direct proportion between the size of the suture material and the reaction zone could, however, not be proved in a series of experiments on rabbits when catgut of Nos. 0000, 000, 00, 0 and 1 was used for the closure of fascial incision wounds. On the other hand, if the diameter of the suture material was disproportionally large (Nos. 4 and 5) a prolonged exudative reaction with aseptic abscess formation was found, not only with catgut but even with cotton and silk. This may explain the mechanism of some of the suture extrusions encountered in patients.

Conclusion. It seems justified to assume that a sufficient knowledge of the histologic reactions around surgical suture materials in wounds can be obtained and a comparison between various kinds of suture materials can be carried out if they are inserted as tied sutures of the same gauge into fascial incision wounds (and in the peritoneum) in rabbits, and excised on the fourth, eighth, and sixteenth day postoperatively for microscopic examination. Infection around the sutures must be excluded previously by bacteriologic control.

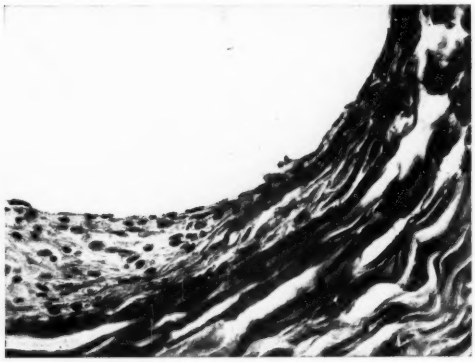

Fig. 11. Detail from Figure 10. Fibroblasts and collagenous connective tissue. ×262.

STANDARD TECHNIQUE

The following standard technique is suggested for a histologic evaluation of buried suture materials in laparotomy wounds: The suture materials to be examined and compared must be sterile and of exactly the same size. Three animals (rabbits) are used for each series of experiments. They are placed on their backs on the operating table. The hairs on the abdomen have been removed on the previous day with barium sulfide. Urethane anesthesia is used. The operation field is protected with sterile towels, and sterile gloves and instruments are used.

In the animal's right obliquus externus fascia a linear incision is made, somewhat away from the skin incision, and the sutures to be examined are inserted at a uniform distance of 1 centimeter apart and tied with a triple knot. Triangular curved needles of the same size are used for all the sutures. The sub-

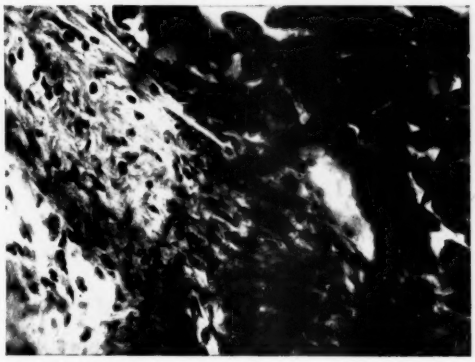

Fig. 13. Higher magnification of detail from Figure 12. Fibroblasts and a few histiocytes, young collagenous connective tissue. ×262.

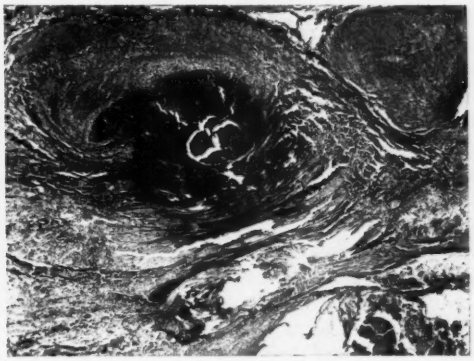

Fig. 14. Tissue reactions around plain catgut in fascia; 10 days postoperatively. Wide reaction zone, marked exudation, fragmentation of suture, slight proliferation. ×24.

cutaneous layer and the skin are closed with continuous monofilament nylon sutures. In the animal's left iliac fossa the peritoneum is opened, and the same suture materials are used for closure of this wound. Rabbit No. 1 is killed on the fourth day, rabbit No. 2 on the eighth day, and rabbit No. 3 on the sixteenth day after operation. The fascial sutures are excised one by one with an appropriate area of the surrounding tissue and prepared for microscopic study. The peritoneum is then opened in the median line, and the peritoneal sutures are examined for adhesions (Fig. 9). (This additional examination was undertaken after it had been found in a considerable number of animals that localized adhesions had formed between the intestines and such sutures around which very distinct exudative reactions could be seen microscopically. That talcum was not a causative factor was demonstrated by polarization microscopy, and allergy could also be excluded.)

RESULTS

In a series of experiments the author has investigated the following suture materials, mainly using the standard technique mentioned: (a) nonabsorbable materials: silk, cotton, linen, hemp, monofilament and multifilament nylon, multifilament stainless steel, and tantalum; (b) absorbable materials: plain catgut, peroxide catgut, iodine catgut, and chromicized catgut of various kinds and brands. The nonabsorbable materials were autoclaved, and none of them was prepared with wax or resins to make them free of noncapillary attraction. All the brands of catgut had been proved sterile by the routine control carried out in the Bacteriologic Department of the University Institute of General Pathology in Copenhagen.

a. Minor variations in the histologic picture could certainly be demonstrated around the different nonabsorbable suture materials, but they did not seem to be of practical consequence to wound healing, as long as they were of a proper diameter. Around all the nonabsorbable suture materials mentioned was characteristically found slight exudation of short duration, quickly appearing fibroplasia

Fig. 15. Detail from Figure 14. Masses of leucocytes, edema, and fibrin, but no histiocytes. ×262.

(after 5 to 6 days) and an early collagenous connective tissue formation (after 10 to 16 days). The reaction zone around the sutures was relatively small. Peritoneal adhesions between these sutures and the intestines were not found, and within the period in which they were examined no fraying of the threads or other alterations could be observed (Figs. 10 to 13).

b. The group of absorbable suture materials displayed much greater variations in the tissue reactions produced, depending mainly on the chemicals used for sterilization or preparation of the threads but also on the quality and purity of the raw material. Both factors influence the molecular structure of the catgut fiber and consequently the foreign body reactions around it.

Plain catgut showed the quickest absorption rate. The sutures were rarely visible after 30 days, either to the naked eye or under the microscope, but even after 5 to 6 days they had become digested to such a degree as to have lost their tensile strength completely. There was constantly found a wide reaction zone and an early appearing, prolonged, and very marked exudation (Figs. 14 and 15). Proliferation became apparent comparatively late, histiocytes and fibroblasts seldom prevailing until after 8 to 10 days. The remaining scar formation did not seem to be marked.

Peroxide catgut sutures were also rapidly absorbed in the tissues; however, traces could be found after 30 days. The reaction zone was somewhat wider while the cellular reactions, upon the whole, were similar to those around plain catgut.

Iodine catgut took a decidedly longer time to become absorbed; in experiments in pigs large fragments of the sutures were still found in the deep layers 70 days postoperatively. Usually a wide reaction zone was observed. Exudation was very marked and prolonged, occasionally with sterile suppurations and peritoneal adhesions between the sutures and an intestinal loop. Fibroplasia was seldom predominant until after 16 days.

Chromicized catgut sutures showed a delayed absorption depending on the chromium concentration with which the thread had been prepared. During the first days after their insertion they behaved almost as nonabsorbable suture materials in the tissues, but when the chromium had disappeared after about 10 to 20 days the sutures quite suddenly produced a marked exudation followed by fibroplasia and scar formation.

DISCUSSION

It must be emphasized that the histologic method gives only limited information about the qualities of the various suture materials, even when a standard technique is used. It is hereby possible to ascertain that some suture materials constantly produce a very marked and prolonged exudation and, therefore, are liable to cause suppuration in the wound, knot extrusion, and intraperitoneal adhesions. It is justifiable to assume that such reactions will cause weakening of the surrounding tissue so that even solid fascia may become soft as cheese. With some exactness it can be deduced from the microscopic appearance that certain suture materials are so rapidly absorbed that the threads will break as soon as they are exposed to increased tension. Exact information, however, cannot be obtained solely by means of the microscope. It is necessary to use more direct methods in order to find out if the various suture materials are able to fulfill their function of holding the edges of the wound together during healing.

EXPERIMENTAL VASCULAR GRAFTS

III. The Dimensional Changes in Short and Long Length Fresh and Preserved Aortic Homografts Implanted into the Thoracic Aorta of Growing Pigs: A Preliminary Report

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THE search for an effective conduit of blood to replace various congenital, traumatic, and other pathologic aortic defects has been subject to renewed interest in recent years. In considering early surgery for congenital abnormalities, such as coarctation of the aorta, the growth or dimensional change of the replacing conduit is of great importance. The ideal vascular implant should keep pace with growth of the host aorta in the growing patient. To investigate vascular growth, the growing pig has been selected for this experimental study. This animal was used for several reasons: easy availability, rapid maturation, large increase in size, and ease of maintenance. This paper presents our preliminary observations on the dimensional changes of fresh and preserved aortic homografts of various lengths implanted into the thoracic aorta of growing pigs.

METHODS AND PROCEDURE

Aortic homografts were implanted into the thoracic aorta of 9 weanling pigs, intraperitoneal nembutal and endotracheal ether anesthesia being used. The average weight of these pigs at operation was 12.4 kilograms. Sterile technique was observed throughout all these procedures. The left pleural cavity was opened through the bed of the fifth rib. Usually one or two ribs were transected posteriorly above or below to facilitate adequate exposure. After satisfactory mobilization of the aorta, the necessary aortic defect was created by excising a suitable segment from between occluding Potts coarctation clamps. A tubular methyl methacrylate (lucite) shunt with the graft sleeved upon it was promptly positioned across the defect and tied into the severed ends of the host aorta. The occluding clamps were removed to restore an adequate distal blood flow while the anastomoses were performed. The type of suture material and method of suture varied in the anastomoses of these experiments. Absorbable and nonabsorbable sutures were used and each anastomosis was performed with either a continuous everting mattress or a continuous Carrel suture. The shunt was removed just prior to completion of the last anastomosis. Suture markers were placed in the host aorta and graft to facilitate accurate linear measurements at eventual necropsy. Upon completion of the operative graft-aortic measurements, the grafted area was covered with flaps of parietal pleura. After a 2 week period of careful observation, the pigs were transferred to a farm where they remained until they reached maturity and were then brought to slaughter. At slaughter the average weight of the 7 pigs that survived to maturity was 109 kilograms, or an average weight increase of 695 per cent. All measurements were made of the adjacent aorta and graft with the specimen inflated with air at a pressure of 120 millimeters of mercury. Plain roentgenograms were taken to demonstrate calcification of certain grafts and, in addition, the

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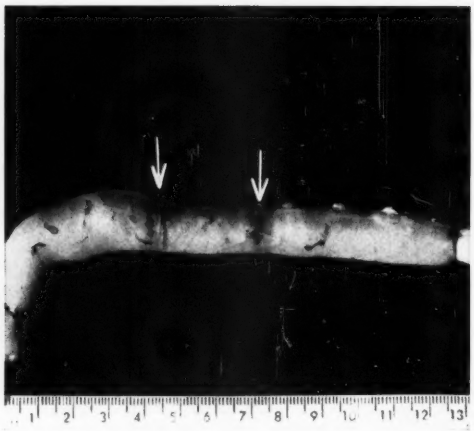

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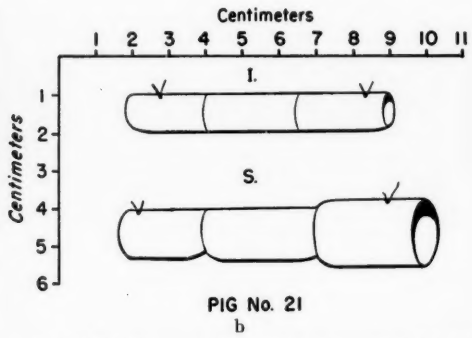

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Fig. 1. a, Short fresh aortic homograft of the thoracic aorta from Pig 21, 79 days after graft implantation. The graft is inflated to 120 millimeters of mercury with air. The arrows indicate the anastomoses. The proximal aorta is on the left. b, Schematic drawing of this graft at implantation and at death. *I* represents the graft at implantation; *S* at slaughter. There is a notable discrepancy between the rate of growth of the graft and the host aorta. Proximal aorta is to the right.

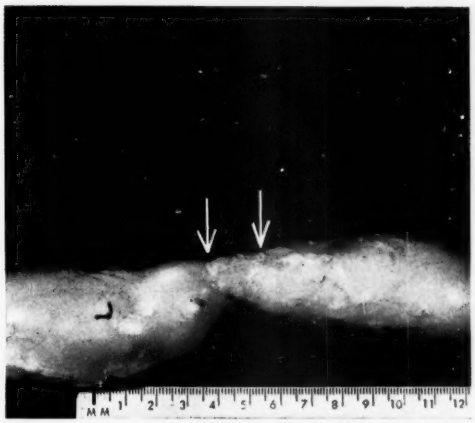
intraluminal contours were determined by x-ray examination of graft specimens filled with 80 per cent sodium iodide solution. Photographs of the vascular transplants, both inflated with air and open, were made and, finally, the grafts were prepared for microscopic study.

An arbitrary definition of graft length was made in this study; those over 5 centimeters at implantation were defined as long grafts. Five aortic homografts used as preserved grafts were collected under aseptic conditions and stored in a sterile solution (Ringer's or Tyrode's with 10 per cent homologous serum) or preserved in mineral oil at a temperature of 4 degrees C. until just prior to implantation. Four fresh aortic homografts were implanted.

TABLE I.—SUMMARY OF THE DIMENSIONAL CHANGES IN FRESH AND PRESERVED AORTIC HOMOGRAFTS OF SHORT AND LONG LENGTH IMPLANTED INTO THE THORACIC AORTA OF GROWING PIGS

Type of graft—Length	Short				Long				
Type of graft—Fresh or preserved	Fresh		Preserved		Fresh		Preserved		
Pig No.	21	37†	17	45	43	53	20	36	52
Per cent increase pig weight	2*	42*	838	561	451	858	645	671	820
Length of graft at implantation in cm.	2.6	4.5	2.4	3.8	10.1	7.0	5.4	8.6	10.8
Preservative and No. days graft preserved	None	None	Mineral oil 243	Mineral oil 27	None	None	Ringer's solution 413	Mineral oil 1	Tyrode's solution 2
No. days graft implanted	79	35	225	192	193	189	218	187	189
Per cent increase graft length	15		85*	5	14	50	18	12	30
Per cent increase aorta length	42			46	84	119	95	134	121
Per cent increase graft external diameter	14		65	13	12	65	41	12	10
Per cent increase aorta external diameter	71		117	50	76	108	99	123	116
Graft/aorta diameter ratio at implantation	1.0	1.0	.74	.92	1.02	1.0	.77	.98	.87
Graft/aorta diameter ratio at slaughter	.66		.56	.69	.60	.68	.62	.46	.39

*Per cent decrease in 2 pigs dying early.
†No measurements taken at necropsy.



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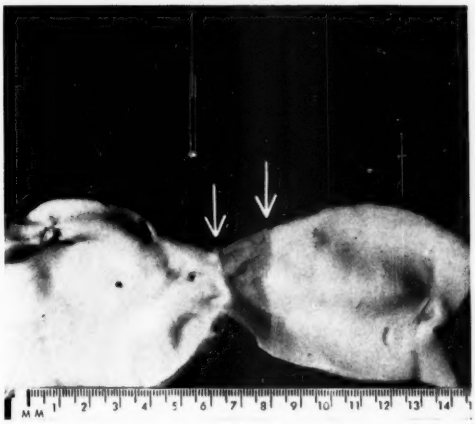

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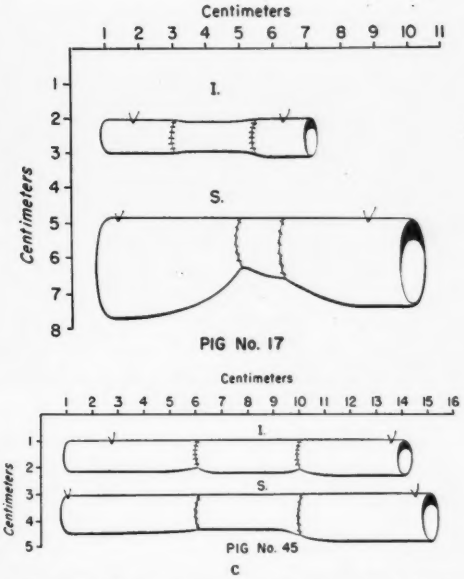

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Fig. 2. a, Short preserved aortic homograft of the thoracic aorta from Pig 17, 225 days after implantation. The arrows indicate the anastomoses. Proximal aorta is on the right. The graft and aorta were measured when inflated to 120 millimeters of mercury with air. There is marked narrowing at the lower anastomosis as seen on the left. There is typical poststenotic dilatation. b, Open view of graft from Pig 17. A fibrous band is seen near the lower anastomosis on the left. The intimal surface is smooth with no evidence of degenerative change although this graft was preserved for 243 days in mineral oil prior to implantation. c, Scale diagrams of both grafts of this group. Proximal aorta is to the right. The sutures represented are at the points on the proximal and distal aorta where the measurements were taken.

RESULTS

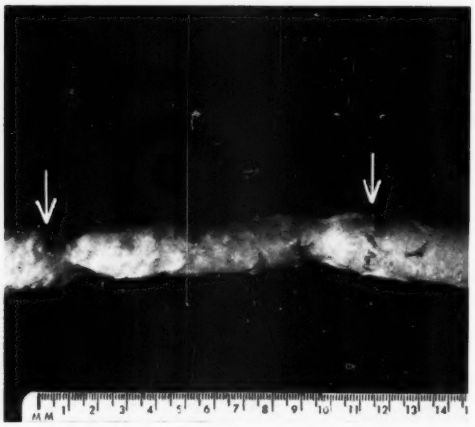
No instance of thrombosis, rupture, or dilatation was present at the time of slaughter. All the grafts were patent. Two pigs died from nongraft complications on the thirty-fifth postoperative day and the seventy-ninth postoperative day. Unfortunately, both of these animals were in the same graft classification, i.e., short fresh aortic homografts. The histologic and degenerative changes observed in these grafts are the subjects of other communications by Kanar and his coworkers and will not be discussed in this presentation. Table I summarizes the dimensional changes of the fresh and preserved aortic homografts of short and long length implanted into the thoracic aorta of growing pigs. For the purposes of this paper, the following criteria will be used to classify the results of grafts as far as constriction is concerned (none of the 9 grafts reported here showed dilatation):

Satisfactory = no constriction.

Partially satisfactory = 1–39 per cent constriction insofar as graft/aorta diameter ratio is concerned.

Unsatisfactory = 40 per cent or more constriction as defined in the same way.

Short length fresh aortic homografts. As noted previously, the 2 animals with such grafts died prematurely. Measurements were not recorded for Pig 37 at autopsy, but the



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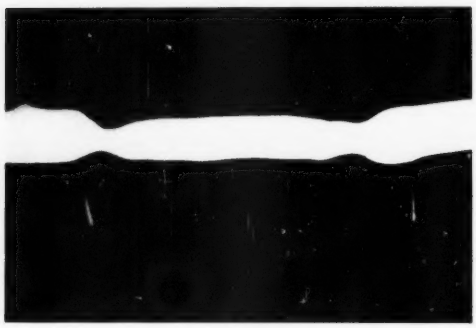

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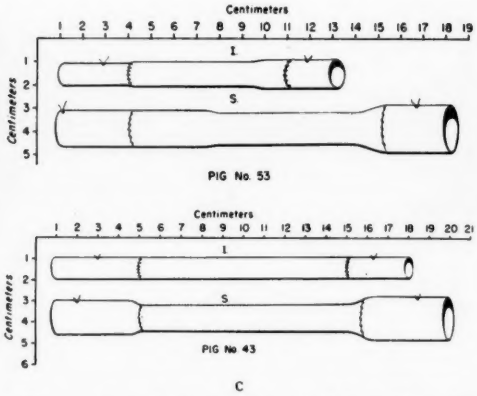

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Fig. 3. a, Long fresh aortic homograft from Pig 53 inflated to 120 millimeters of mercury with air. The homograft is between the arrows and the proximal aorta is to the right. The implant increased in external diameter 65 per cent and at slaughter had a graft/aorta diameter ratio of .68. b, An x-ray film of the graft from Pig 53 filled with 80 per cent sodium iodide solution. There is moderate stenosis near the distal anastomosis as seen above the marker on the left. c, The diagrams show enlargement of the grafts from implantation to slaughter, but not as much as the adjacent aorta.

graft appeared to be isodimensional. Although Pig 21 died a relatively short time after graft implantation, it was already apparent that growth of the implanted segment was not keeping pace with that of the adjacent aorta. The appearance of this graft is illustrated by diagrams and photographs in Figure 1a and 1b.

Short length preserved aortic homografts. There was a 65 per cent increase in the external diameter of the implant in Pig 17, however, the presence of a web-like intimal band at the lower anastomosis gave a distorted appearance. The etiology of this band and failure of the graft to increase in length cannot be explained from the gross and microscopic studies. This particular graft is shown inflated with air and open in Figure 2a and b. Although this graft had been preserved for 8 months in mineral oil, no obvious degenerative change was present. The second graft of this series in Pig 45 had a graft/aortic diameter ratio of 0.92 at implantation, whereas, at slaughter, this ratio was 0.69. The external diameter of the graft increased 13 per cent. The implant can be considered to be only partially satisfactory because of the 31 per cent discrepancy between the aorta and itself. A diagrammatic representation of the latter two grafts is shown in Figure 2c.

Long length fresh aortic homografts. The external diameter of the grafts from Pigs 43 and 53 increased 12 and 65 per cent. The grafts were respectively 40 and 32 per cent smaller than the adjacent aorta and may be considered as partially satisfactory. A photograph of the graft from Pig 53 is seen in Figure 3a. Figure 3b illustrates the internal contour of this implant, while Figure 3c is a diagram of both of these grafts at implantation and slaughter.

Long length preserved aortic homografts. The 2 vascular implants in Pigs 36 and 52 failed to increase sufficiently in external diameter with probable impedance of blood flow. One

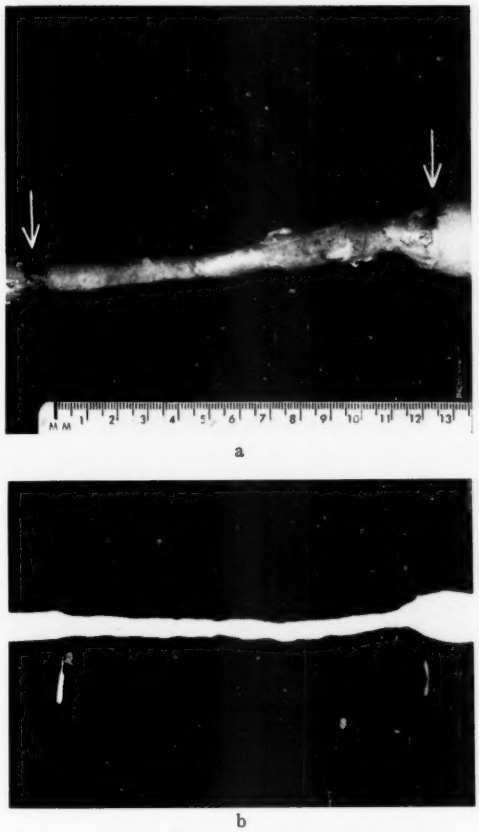

Fig. 4. a, Long preserved aortic homograft from Pig 52 is shown between the arrows. Proximal aorta is to the right. It is inflated to 120 millimeters of mercury with air. The graft external diameter increased 10 per cent in contrast to 116 per cent increase of the adjacent aorta. b, X-ray film of this graft filled with sodium iodide solution. The markers are at the anastomoses.

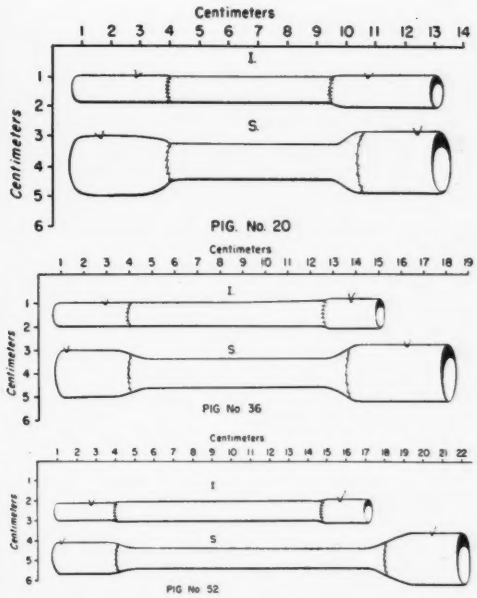

Fig. 5. Scale drawing of the long preserved aortic homografts in these experiments. Only 1 of these, that implanted in Pig 20, can be considered as partially satisfactory with respect to dimensional change.

of these is shown in Figure 4a and b. Figure 5 is a diagrammatic illustration of the 3 grafts of this group. It is interesting that the transplant, the diameter of which had increased 41 per cent (Pig. 20), had been preserved over 1 year, whereas, the transplants in Pigs 36 and 52 had been preserved for only 1 and 2 days respectively.

COMMENT

Surgical replacement of segments of the thoracic aorta may be necessitated by the occurrence of pathologic processes such as aneurysms, neoplasms, traumatic injuries, and congenital malformations. The clinical importance of graft enlargement relative to coarctation of the aorta is obvious, particularly if operative intervention takes place at the age of 2 or 3 years. If a graft is necessary to bridge the defect caused by excision of a constricted segment of aorta, it probably would be short or less than 5 centimeters in length. Johnson and Kirby (3) reported that in the abdominal aortas of 4 growing pigs, short (2.5 cm.) fresh aortic homografts could equal the growth of the host aorta. Everson and Southwick (1) in similar studies found that in 2 of 3 short (1.5 to 2.2 cm.) preserved aortic homografts of the abdominal aorta, the rate of growth was equal to that of the adjacent aorta. Johnson and Kirby (4) implanted 9 short (2.5 cm.) preserved aortic homograft segments in the abdominal aortas of young pigs. There was limitation of growth in all but 1, which was dilated.

It would appear from these observations that in the abdominal aorta partially satisfactory growth occurs with short length fresh and preserved aortic homografts. Reference to Table I will show that in short grafts of the types noted in the thoracic aorta in our experiment, growth both in length and external diameter did occur, but the rate of graft enlargement did not match that of the host aorta. The obvious question is whether there was sufficient increase in diameter of the implant to prevent relative constriction with resultant impeded and turbulent blood flow. As shown by Mann, Herrick, Essex, and Baldes, significant reduction of blood flow does not occur prior to a decrease of 40 per cent in the external diameter of a given vessel. Using this criterion, only 1 of the short grafts, that in Pig 17, would be unsatisfactory. This transplant had a 65 per cent increase in external diameter at slaughter, but the graft/aortic diameter disproportion (0.74) created at implantation could not be overcome. Gross stated that "a graft should be selected which is of the same size or possibly slightly larger than the aorta into which it is fitted."

The growth factor in long aortic homografts of the thoracic aorta has not been thoroughly investigated. McCune and Blades believed that long (over 18 cm.) preserved aortic homografts implanted in adult dogs give as good, if not better, results than short grafts of the same type. If the known fibroplastic ingrowth from the recipient aorta can completely bridge a graft of such length, one might speculate that it could also promote sufficient growth in the relatively shorter grafts as used in our experiments. This has been partially borne out by this small series of long grafts. Both of the long length fresh and one of the long length preserved grafts had partially satisfactory dimensional changes. The finding of Sauvage and Harkins that the duration of preservation did not alter significantly the tendency of grafts to enlarge was observed here. The only 1 of the 3 long preserved grafts which could be considered as partially satisfactory (39 per cent or less undersize in diameter) had been preserved for over 13 months, whereas, the 2 which were unsatisfactory (more than 40 per cent undersize) had been preserved for 1 and 2 days.

The relationship of vascular growth in the fast growing animal to similar growth in the more slowly growing human is unknown. This factor must be considered when attempting to evaluate our experimental work in clinical terms. From these preliminary findings it would appear that some enlargement of grafts can take place but, as a generality, thoracic aortic homografts tend to lag behind the growth of the host aorta, irrespective of the graft length or duration of preservation.

SUMMARY

1. A preliminary report of the growth factor of aortic homografts implanted into the thoracic aorta of 9 growing pigs is presented.

2. The method of study is reviewed.

3. The probability that duration of graft preservation does not significantly alter graft growth is confirmed.

4. In the short and long, fresh and preserved thoracic aortic homografts in these experiments growth did occur, but at a slower rate than that of the host aorta.

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THE ANATOMIC BASIS FOR ISCHEMIA LOCALIZED TO CERTAIN MUSCLES OF THE LOWER LIMB

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WE ARE accustomed to the thesis that in most instances a viscus depends upon an individual artery. Thus we find no paradox in seeing necrosis of the bowel caused by obstruction of a mesenteric artery, while blood flow continues through the aorta to more distal parts. The existence of collateral pathways in the limb causes us to overlook the fact that here too, some structures may depend completely, or in large part, on individual branches of the main arterial stem. Of the various tissues of the limb certain of the muscles, by virtue of the pattern of their arterial supply, are particularly prone to ischemia through interruption of such branches. That the resultant ischemia may give rise to necrosis of a muscle or muscle group, while the remainder of the limb remains unaffected, has been known to some observers. Examples of necrosis of individual muscles through wounding of their nutrient arteries occurring in World War I were reported by Campbell and Pennefather and in World War II by Power. Necrosis of the anterior tibial group of muscles alone, due to ischemia in their compartment has likewise been described as of occasional occurrence by Hughes and others. In our clinic we have noted that even more frequent examples of acute and chronic localized muscle ischemia are to be found in patients with occlusive vascular disease, particularly arteriosclerosis (6).

The anatomic basis for such localized necrosis is the dependence of each muscle upon a single arterial source. This was touched on by Spalteholz who showed that the circulation of a muscle was quite distinct, and devoid of significant connections with the vessels of neighboring structures. Wollenberg surveyed briefly the arterial supply to the muscles of the lower limb. A more comprehensive examination was later undertaken by Campbell and Pennefather. The classification given herein is similar to the one they suggested. The present report records in somewhat greater detail through illustration, the arterial supply of each of the muscles of the lower extremities, as determined by dissection, and correlates the anatomy with clinical syndromes of localized muscle ischemia.

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DISTRIBUTION OF ARTERIES TO THE MUSCLES

The muscles may be classified in the following three categories with respect to their nutrient arteries.

1. Those receiving branches from several sources. The iliopsoas, for example, is supplied from the subcostal, 4 lumbars, the iliolumbar, deep circumflex iliac, external iliac, femoral, and lateral femoral circumflex arteries (Figs. 1, 3).

2. Those possessing a series of arteries derived from a long segment of one major trunk. Examples are the sartorius, and the vastus medialis, which are thus supplied by the superficial femoral artery (Fig. 3) and the tibialis anterior which the anterior tibial artery alone supplies (Fig. 7).

3. Those supplied by one or a few branches arising in a sharply localized segment of one arterial trunk. In this category are the rectus femoris, receiving its nutrient vessels from the lateral femoral circumflex artery (Fig. 4), and each head of the gastrocnemius similarly supplied by the popliteal artery (Fig. 5).

Variations in the arterial pattern may determine differences in response to vascular interruption. The exact number of arteries entering a muscle will vary somewhat from one subject to another, neighboring vessels sometimes supplying branches not seen in the majority of individuals.

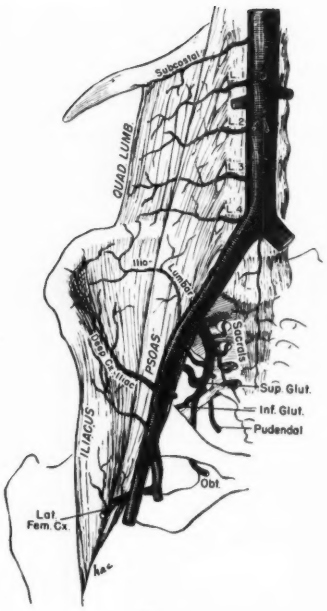


Fig. 1.

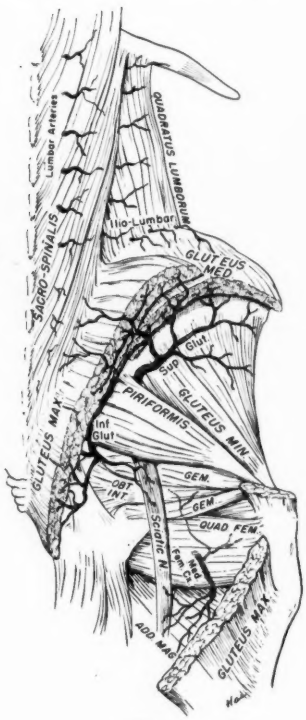


Fig. 2.

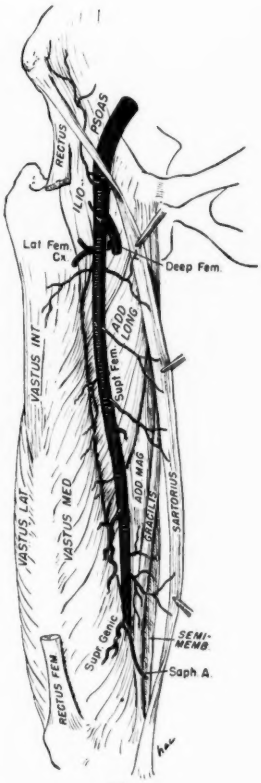


Fig. 3.

Fig. 1. Distribution of the lumbar arteries and the parietal branches of the hypogastric artery, anterior view, to the iliopsoas and the quadratus lumborum muscles.

Fig. 2. Distribution of the lumbar arteries and the parietal branches of the hypogastric artery, posterior view, to the muscles of the hip as well as to the lower part of the sacrospinalis muscle.

Fig. 3. Distribution of the superficial femoral artery. The sartorius is entirely dependent on this vessel, the vastus medialis muscle largely so.

Of still greater significance are the variations in origin of the larger arterial branches with respect to the main stem. These variations are treated in considerable detail in the work of Adachi. Some of the more outstanding facts may be noted here.

The iliolumbar artery may arise from the superior gluteal rather than the hypogastric in less than half the instances. In 25 per cent the iliac and lumbar branches are distinct, the iliac arising most frequently from the superior gluteal or obturator arteries, the lumbar from the hypogastric. The lumbar branch may be large and replace the fourth lumbar artery or be missing, a fifth lumbar artery arising from the aorta or middle sacral to replace it.

The obturator artery originates from the external iliac or the inferior epigastric in about 30 per cent. There is great variation in the pattern of branching of the femoral artery. The medial femoral circumflex artery arises separately from the common femoral in approximately 22 per cent; the lateral circumflex separately from the common femoral in 18 per cent; both circumflex arteries separately in 5 per cent. Rarely either circumflex artery may arise from the external iliac artery. The descending branch of the lateral femoral circumflex arises from the superficial femoral in 11 per cent.

The medial femoral circumflex artery is occasionally small. In these instances a larger

inferior gluteal artery is more widely distributed to the posterior thigh muscles and the sciatic nerve.

A reciprocal relationship exists in the size of each of the three major vessels in the leg, that is, the anterior tibial, posterior tibial, and peroneal arteries. When one is exceptionally large, the others are smaller. Moreover, the anterior tibial is often abridged and fails to reach the foot. In these instances the perforating branch of the peroneal continues as a dorsalis pedis artery, either alone, or by anastomosis with the anterior tibial. Similarly the peroneal may replace or strengthen the lower part of the posterior tibial artery (Fig. 6). The precise frequency of these variations has not been recorded.

Certain special attributes of the arterial supply of muscles explain their liability to ischemia.

1. The circulation of a muscle, especially as regards the arteries, is an isolated unit, the nutrient artery having no substantial connection with vessels of neighboring structures. The veins possess somewhat more anastomoses. Occasional exceptions are noted; for example, branches of the perforating arteries coursing to the hamstrings and vasti often bifurcate to supply two neighboring muscles. Similarly some branches of the peroneal artery run to the flexor hallucis longus as well as to the peronei (Fig. 8). Wollenberg has demonstrated that the intramuscular vessels are continuous with those of the tendon, and thus with fine arteries derived from neighboring fascia and joint capsules. In many areas, muscle arteries send branches to the fascial septa and to the skin, but these branches are extremely fine and, as Spalteholz noted, could be expected to act as collaterals only to the connective tissue of the muscles.

2. When the muscle arteries are multiple, they may enter the muscle at regular intervals or rather at one localized site, where injury may involve all at once.

3. No anastomoses exist external to the muscle between a number of arteries supplying that muscle.

4. An intramuscular network of anastomoses between branches of the arteries does exist, but as Clark and Blomfield have shown it is often of a pattern which makes ischemia probable after occlusion.

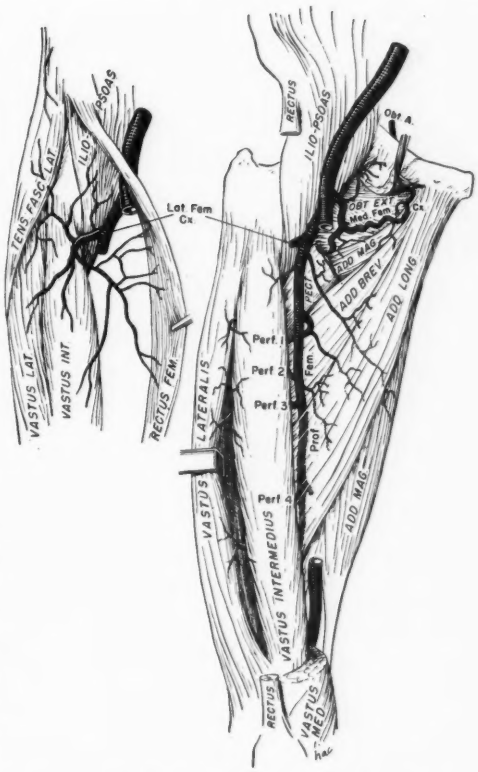


Fig. 4. Distribution of the profunda femoris artery, anterior view, to the adductor and quadriceps muscles. The rectus femoris is entirely dependent on the lateral femoral circumflex branch.

CLINICAL SYNDROMES DUE TO LOCALIZED MUSCLE ISCHEMIA

Necrosis in acute arterial obstruction. The pattern of ischemic necrosis of the muscles varies according to the territory supplied by the interrupted artery (Fig. 11). If the main trunk is involved, with resultant gangrene, one expects death of all the muscles in the gangrenous part of the limb. Even in such distal necrosis, the upward limit of death of some muscles may lie far above that of other muscles or of the skin, because of the varying site of origin of specific muscle arteries.

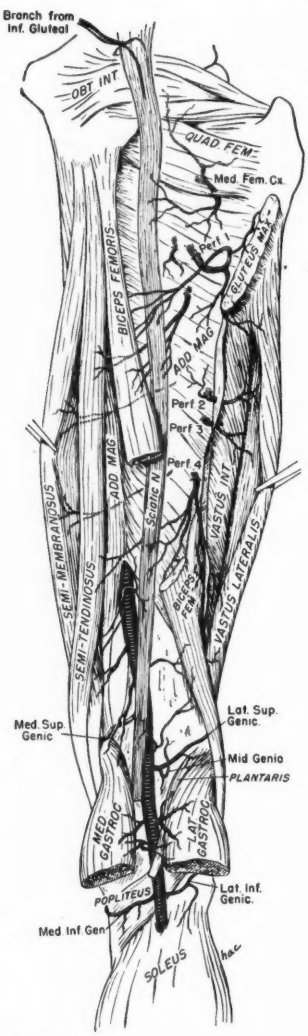


Fig. 5. Distribution of the profunda femoris artery, posterior view, and of the popliteal artery. The distribution of the profunda femoris to the hamstring muscles and sciatic nerve is shared by the popliteal artery, and in some subjects by the inferior gluteal artery.

The following 2 case reports illustrate such high necrosis in occlusion of the femoral and popliteal arteries respectively.

CASE 1. A 79 year old man suffered an embolism of the right common femoral artery as a result of arteriosclerotic heart disease and auricular fibrillation. Embolectomy 8 hours later was unsuccessful in restoring the circulation of the limb, because of extensive secondary thrombosis in the common and superficial femoral arteries.

Gangrene followed, with a line of demarcation at midthigh level. The sartorius, vastus medialis, and rectus femoris muscles were, nevertheless, necrotic above this level quite to their origins. The death of the first two of these muscles in their entirety could be correlated with thrombosis of the entire length of the superficial femoral artery; and the necrosis of the whole rectus femoris was explained by occlusion of the origin of the lateral femoral circumflex artery (Fig. 11a). The remaining muscles all showed good blood supply above the midthigh level, associated with patency of the deep femoral artery beyond its origin. Blood from collateral channels could apparently thus reach the nutrient vessels of the viable muscles.

CASE 2. A 50 year old man developed a sudden thrombosis of the lower 3 inches of the popliteal artery during hospitalization for arteriosclerotic heart disease and failure. Replacement of the thrombosed segment by an arterial homograft resulted in new thrombosis and gangrene. The limb was amputated at midleg level. One week later the entire gastrocnemius muscle above this level sloughed, and was lifted out of the reopened incision. The remaining tissues were viable.

The patient followed a downhill course, with a new thrombosis of the left external iliac and upper femoral arteries, amputation of the left leg, and sudden death, 7 weeks after the onset of his illness. Autopsy revealed an old myocardial infarction with mural thrombosis, old rheumatic heart disease of the mitral valve, a small, old infarct of the right lung, and severe nephrosclerosis.

Localized ischemia due to obstruction of branches of the main stem may cause the death of varying portions of the musculature. A group of muscles may be affected, as in the necrosis of the entire anterior tibial group following the injury or obstruction of the anterior tibial artery (Fig. 11b).

CASE 3. A young infantryman was seen in an evacuation hospital in Italy during World War II, 1 day after he had suffered a penetrating shell fragment wound of the right leg. The wound was small, and located lateral to the tibia, about 3 inches below the patella. The skin over the anterior tibial compartment was violaceous in color; this area was swollen and hard. The foot could not be dorsiflexed, and the dorsalis pedis pulse could not be felt on this side.

The wound was explored, revealing a small shell fragment in contact with the anterior tibial artery, which was thrombosed in its entire length. The three muscles of the compartment were entirely necrotic. The skin incision was extended to the

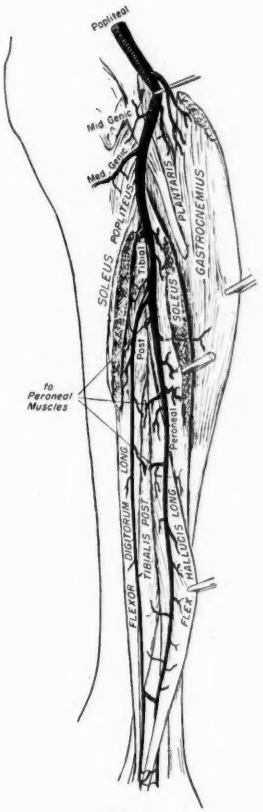


Fig. 6.

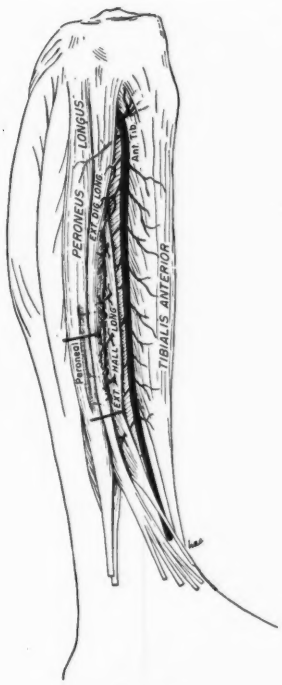


Fig. 7.

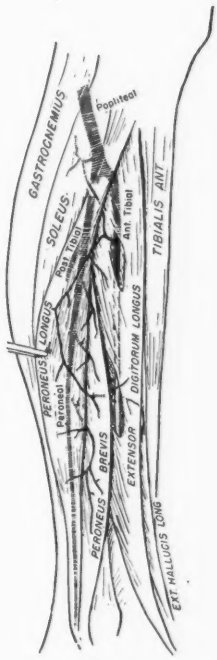


Fig. 8.

Fig. 6. Distribution of the popliteal and posterior tibial arteries. The posterior tibial is unusually small beyond its peroneal branch. The peroneal offers a supernumerary artery to the gastrocnemius muscle. (The usual supply of but one artery to each head of the gastrocnemius muscle is shown in Fig. 5.) The soleus and tibialis posterior muscles receive branches from both the posterior tibial and peroneal arteries. The flexor digitorum longus is supplied by the posterior tibial, and the flexor hallucis longus by the peroneal artery, alone. Some of the latter branches continue to the peroneal muscles (see also Fig. 8).

Fig. 7. Distribution of the anterior tibial artery, from the same subject as Figure 5, but not as in Figures 6 and 8. The artery is the sole source of supply to the tibialis anterior muscle, and is only slightly aided by the peroneal artery in its supply of the extensor digitorum longus and extensor hallucis longus muscles. The anterior tibial artery also aids in supplying the peroneal muscles (see also Fig. 8).

Fig. 8. Distribution of the branches from the peroneal and anterior tibial arteries to the peroneal muscles, from the same subject as in Figure 6.

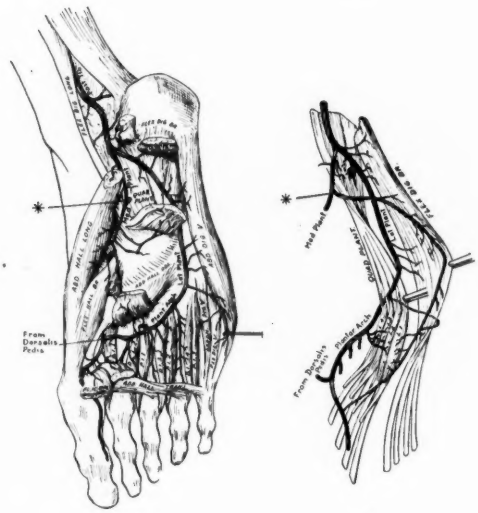
ankle, and the muscles, the anterior tibial vessels, and the deep peroneal nerve were all removed. There resulted a viable, comfortable limb, but with foot drop that remained to be corrected later.

Necrosis of an entire single muscle alone is possible when it is supplied from one vessel or a small group of vessels from a localized source. Examples are necrosis of the rectus femoris, or of one head of the gastrocnemius, following gunshot wounds of the artery supplying either of these muscles (Fig. 11c). The attachments of the muscle are often spared due to anastomoses here with the vessels of the related fascia or capsule.

Case 4. Another infantryman was seen in a general hospital in France, 2 or 3 days after wounding of the left thigh by a shell fragment. Débridement had previously been performed at another hospital. The patient had some fever. The limb showed an open débridement wound about 5 inches long in the anterior upper thigh. The base of the wound was clean except in its upper and lower parts, where some nonviable muscle could be seen.

The wound was explored. A large portion of the rectus femoris muscle had evidently been removed,

Fig. 9.



a b

Fig. 10.

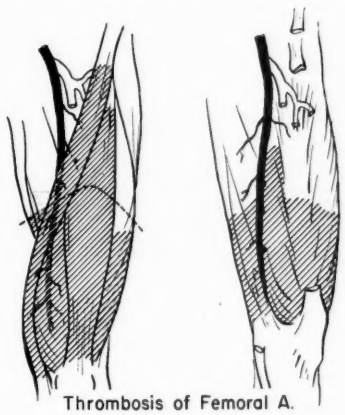
Fig. 9. Distribution of the dorsalis pedis artery to the extensor digitorum brevis and dorsal interosseus muscles. The latter muscles are additionally supplied by the deep plantar arch (Fig. 10). The dorsalis pedis artery is replaced, in some instances, through its anastomosis with the perforating branch of the peroneal seen at the ankle, or similarly through the deep plantar arch from the posterior tibial artery.

Fig. 10. Distribution of the medial and lateral plantar arteries to the muscles of the sole of the foot. The insert on the right (b) shows the distribution of these vessels to the flexor digitorum brevis and quadratus plantae muscles. The entire lateral plantar, and the deep part of the medial plantar arteries are again shown in the main figure on the left (a).

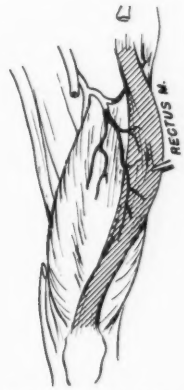
but the upper and lower portions still remained and were necrotic almost to their bony attachments. The lateral femoral circumflex artery had been divided and ligated close to its origin, and the remainder of this vessel removed. Débridement of the remaining necrotic muscle was followed by subsidence of the fever, and a secondary closure was effected several days later.

It is evident clinically, that even in the case of muscles receiving a sharply demarcated supply, the results of localized arterial damage may vary greatly. The gross death of a muscle predicted on anatomic grounds is more certain to occur if the responsible arteries are widely occluded or excised, thus removing pathways for even remote anastomoses. Concomitant physiologic changes such as shock or vasospasm are also important in determining the death of the muscle. Contrariwise, if conditions are favorable, anastomoses of a major trunk with another, or the fine connections of muscle arteries with those of the fascia and skin may modify the ischemia so that only a focal necrosis is produced. This is the same type of necrosis also seen in moderate ischemia after occlusion of the major trunks, as in arteriosclerosis, and possibly, after division of some of the muscle arteries in surgical exposures (Fig. 11d). The process has been admirably described by Bowden and Gutmann. The necrosis involves fasciculi or individual muscle fibers and is best appreciated microscopically. It results in replacement of the involved parts of the muscle by the less demanding connective tissue, which is then often visible to the naked eye as a patchy or interstitial fibrosis.

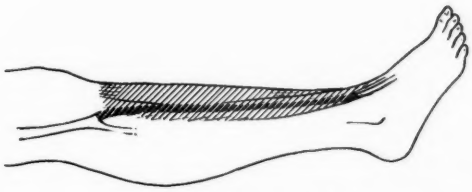
Without surgical exposure, necrosis of a muscle, whether massive or focal, may be recognized through its becoming painful, swollen, and hard. Pain arising in muscle has been studied by Lewis, Pickering, and Rothschild and by Kellgren. The pain is felt partly



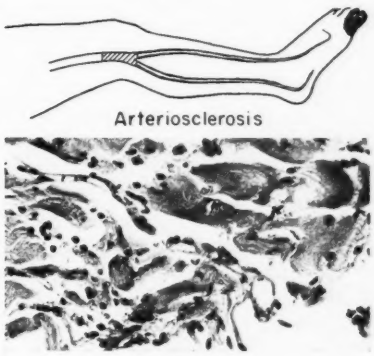
a, Distal.



c, Unitary.



b, Group.



d, Focal.

Fig. 11. Examples of ischemic muscle necrosis. a, Thrombosis of origin of deep femoral artery and of entire length of superficial femoral artery (Case 1). In the figure on the left, the dotted line indicates the level of demarcation of gangrene of most of the tissues. The sartorius and rectus femoris muscles are, however, necrotic to higher levels. On the right, at a deeper level, the vastus medialis is also necrotic above the remainder of the limb. b, Necrosis of the anterior tibial muscle group after anterior tibial artery thrombosis (Case 3). c, Necrosis of rectus femoris muscle from injury of lateral femoral circumflex artery (Case 4). d, Focal necrosis of gastrocnemius muscle after thrombosis of arteriosclerotic popliteal artery. Gangrene was limited to the first and second toes.

over the muscle but more widely over a zone corresponding only approximately to the dermatome belonging to the nerve segment from which the muscle is innervated. Our clinical observations on the location of pain arising in various muscles of the lower limb correspond to the experimental results of Kellgren. Pain arising in the lower sacrospinalis is felt over the muscle and the buttock; from the quadriceps and adductors it is referred to the front of the thigh and to the shin; from the glutei to the lower buttocks and posterior thigh; from the calf muscles directly over the calf and over the posterior thigh; from the peronei over the lateral leg and thigh; from the anterior tibial muscles over the lateral leg and ankle; and from the short muscles of the foot mainly locally, but with some spread to higher areas of the leg. The contracture wears off in a day or so through autolysis, leaving the muscle absolutely flaccid; it disappears less rapidly if improvement in blood flow allows a resolution, presumably always with some fibrosis.

Chronic effects of localized muscle ischemia in arteriosclerosis. Obstruction of arteries to specific muscle groups, out of proportion to involvement of the main trunk, is responsible

for certain atypical effects in arteriosclerosis considered in detail in a previous report (4).

Claudication may be complained of although the pedal pulses are palpable. The symptoms can be explained by occlusion limited to the arteries supplying the muscles involved. The diagnosis is based on the typical nature of the claudication and is aided by the finding of pulse inequality in the two limbs, a systolic murmur over the major arteries, or by some signs of ischemia in the feet.

Claudication pain and atrophy located in the hips, thighs, and lumbar region are usually attributed to obstruction of the lower aorta. From the anatomy, it is apparent that the symptoms may be produced by occlusion only of the parietal branches of the lower aorta and of the hypogastric artery. Clinically this syndrome is thus often unilateral and is sometimes accompanied by patency of the femoral artery.

A syndrome is likewise recognizable due to obstruction of the deep femoral artery. Here the symptoms are located in the adductor region and in most cases in the quadriceps as well. That the quadriceps may escape involvement probably depends on the origin of the lateral femoral circumflex artery from the common femoral in 18 per cent.

The lack of significant collaterals for the muscle arteries is at least one factor responsible for the frequent lack of amelioration of claudication after sympathectomy.

SUMMARY

The arterial supply of each muscle of the lower extremity, as revealed by dissection, is presented. The observation by previous authors is confirmed that the arterial supply to each muscle is essentially distinct from that to neighboring structures. The muscles vary in the number of arteries supplying them. Some are supplied by only one artery, some by several branches from a sharply localized segment of one of the main arterial trunks, while others are supplied by branches from multiple sources.

Necrosis, either of a muscle group, a single muscle, or of multiple foci within a muscle, may thus be occasioned by obstruction or division of a muscle artery, or of some branch of the main arterial stem, while the remainder of the limb remains unaffected. Clinical examples of such occurrences are cited.

Similar, though less profound, localized ischemia explains claudication in arteriosclerotic patients whose pedal pulses are palpable; it is also the basis for claudication pain in atypical locations in these patients. The lack of significant collaterals for the muscle arteries is at least one factor responsible for the frequent lack of amelioration of claudication after sympathectomy.

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COIN LESIONS OF THE LUNG

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THE IMPORTANCE of small, round, solitary, circumscribed pulmonary lesions which give rise to no symptoms has only recently begun to be appreciated. The practice of taking routine survey chest roentgenograms, widely adopted within the past few years, has made it apparent that such lesions are encountered rather frequently. Moreover, each discovered case demands an opinion as to its management. An increasing interest in these nodules has been stimulated principally by the following four facts: (1) Histologic examination has provided proof that they are malignant in a significant percentage of cases. (2) Accumulated experience has shown that pulmonary tuberculomas, which these lesions often prove to be, are best treated by resection. (3) Convincing evidence has been gathered indicating that such masses almost always warrant removal on their own merits, even though they prove to be neither malignant nor of tuberculous origin. (4) Advances in anesthetic and thoracic surgical techniques have occurred which now make it possible to remove silent pulmonary nodules of this type with involvement of little risk to the patient.

The purpose of this paper is to report a series of 40 consecutive coin lesions of the lung in which the diagnosis was histologically verified. In almost all of the patients the mass was surgically excised. Our experience tends to provide support for those who maintain that these localized masses of uncertain etiology may be removed with ease and safety. We also wish to emphasize again the point that by removing them promptly after their discovery a number of lung cancers will be removed in their early, asymptomatic, and possibly curative stage.

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The opinions and assertions expressed herein are the private ones of the authors and are not to be construed as official or to reflect the views of the Navy Department or the naval service at large.

DEFINITION

There appears to be a real need for defining this type of lesion so that comparable studies can be evaluated as to: the incidence of cancer, the significance of calcification, the mortality and morbidity rates following surgical treatment, and the fate of patients with nodules of this type who are treated by observation only. The following limiting criteria are proposed: (1) 1 to 5 centimeters in size, (2) round or oval in shape with sharply circumscribed borders, (3) surrounded on all sides by normal appearing lung, (4) producing no symptoms, (5) homogeneous in density or containing calcium, and (6) solitary.

The foregoing definition would restrict the lesions to those which are small in size, round in shape, smooth in outline, and sharply demarcated from the surrounding lung. Any limitation as to size is admittedly an arbitrary one. It is in the group of small lesions, however, that the most difficulty is encountered in arriving at an accurate preoperative diagnosis. In addition, the proper management of patients with these small masses is more controversial than in cases in which the lesions are of larger size. The inclusion of larger masses would inevitably weight the statistics unduly in regard to malignancy; if smaller lesions were to be included, large Ghon's tubercles would have to be differentiated. The fact that an aerated lung can be seen on all sides of the lesion establishes its intrapulmonary location, thus excluding hilar, mediastinal, and chest wall masses. Hilar masses and those adjacent to the chest wall or mediastinum represent different problems and must be excluded from a discussion limited to peripheral round lesions. One would not expect these small pul-

TABLE I.—INCIDENCE OF CANCER IN COIN LESIONS OF LUNG

Author	No. of cases	No. malignant	Per cent malignant
Davis and Klepser	67	37	55.0
Harrington	16	7	43.8
O'Brien, Tuttle, and Ferkaney	21	9	42.9
Abeles and Ehrlich	21	8	38.0
Fink	30	10	33.3
Sharp and Kinsella	55	15	27.3
Husfeldt and Carlson	33	7	21.2
Effler, Blades, and Marks	24	4	16.6
Mahon and Forsee	55	4	7.3
Storey, Grant, and Rothmann	40	7	17.5
Totals	362	108	29.8

monary nodules to give rise to symptoms. When symptoms are produced, the wisdom of early surgical investigation is not often seriously questioned. It appears advisable, therefore, to restrict the masses under this definition to those which are clinically silent. Calcium may or may not be present within the nodule. Unless multiple round lesions are excluded by definition, an inordinately high percentage of metastatic malignant disease will be encountered in any large series of cases. Hence, only solitary lesions are included. The fact that these masses appear to be round in the posteroanterior chest roentgenogram has caused the term "coin lesion" to be applied to them. As Fink has pointed out, this name is misleading, for their rounded appearance in the lateral view shows that they are spheroid rather than disc shaped. Nevertheless, the name is both adequately descriptive of their roentgenographic appearance as seen in the usual survey film and well understood by the profession. It is not an ideal term but is one that has achieved acceptance by common usage.

REVIEW OF THE LITERATURE

Graham and Singer in 1936 and Alexander in 1942 advocated thoracotomy as the only reliable means of establishing a definitive diagnosis in circumscribed lesions of the lung. Alexander disavowed the erroneous belief, then prevalent, that such lesions are generally benign. He stated that "with rare exception, circumscribed neoplasms within the chest are usually malignant." There seems to be little doubt that he was referring, in general, to larger lesions. The masses shown in his illustrations were of much greater size than in those which we are now considering.

At least 12 papers dealing with coin lesions have appeared in the literature within the past 5 years. The reported incidence of cancer varies from 7.3 per cent to 55 per cent (Table I).

It is of some importance to point out, in view of these wide variations, that no one series of reported cases can be properly compared with another, for all of them are selective on one basis or another. One author will include only asymptomatic tumors, while another reports all coin type lesions, regardless of the presence or absence of symptoms. For example, Husfeldt and Carlsen, who included only asymptomatic cases, encountered cancer in but 21.2 per cent of 33 cases and Effler, Blades, and Marks, whose patients were also free of complaints, found malignant neoplasms in only 16.6 per cent of 24 patients. On the other hand, Davis and Klepser reported a cancer rate of 55 per cent in a group of 67 patients, including those with pulmonary symptoms as well as those who were symptom-free. The lesion produced symptoms in 28 of 37 (76 per cent) patients with a malignant tumor, while there were symptoms in only 7 of 30 patients (23 per cent) in whom the mass proved to be benign. Just 6 of the 21 patients (28.9 per cent) who were reported by O'Brien, Tuttle, and Ferkaney were free of symptoms, and in that series the cancer rate was 42.9 per cent.

In some reports a limitation is placed upon size, while in others all round, solitary, circumscribed pulmonary lesions are included, regardless of their dimensions. Sharp and Kinsella noted malignancy in but 27 per cent of 55 solitary pulmonary nodules ranging in size from 1 to 4 centimeters in diameter, while a cancer rate of as high as 55 per cent has been reported in other series which included all round circumscribed lesions irrespective of size. In a consideration of the larger tumors only, Thornton, Adams, and Bloch found 78.3 per cent of 23 patients with "cannon-ball" tumors, measuring at least 2 inches in diameter, to have a malignant lesion.

Certain reports have been selective in that patients of a particular age and sex group have predominated while others have represented a cross section of the general population. The patients comprising the series reported by Effler, Blades, and Marks came from a young group of males of military age and those of Mahon and Forsee also represented chiefly males in early middle life. Those two series showed a cancer rate of 16.6 and 7.3 per cent, respectively. The patients of Davis and Klepser, Harrington, and O'Brien, Tuttle, and Ferkaney were unselected as to age or sex and they showed, in order, an incidence of cancer of 55 per cent, 43.8 per cent, and 42.9 per cent. Reports from hospitals devoted particularly to the treatment of patients with pulmonary tuberculosis would be expected to include a higher percentage of tuberculomas, and conversely, a lower percentage of cancer. Patients with associated evidence leading to the suspicion that the lesion was of tuberculous origin would be more apt to be transferred to such an institution. The assumption appears to be borne out by the experience of Mahon and Forsee (7.3 per cent cancer) and the series reported herein (17.5 per cent cancer). Fitzsimmons General Hospital, the source of Mahon and Forsee's material, is an Army center for the treatment of patients with pulmonary tuberculosis, while this hospital serves the Navy in the same capacity.

The cancer rate in coin lesions has varied from a low of 7.3 per cent to a high of 55 per cent in a series of 10 reports, including the present one, which have appeared in the literature within recent years (Table I). Some of the reasons for these variations have already been discussed. Due to the tendency of bronchogenic carcinoma to arise in the larger bronchi, the inclusion of masses adjacent to the hilum would obviously increase the percentage of cases in which malignancy is found. Tumors located in the superior pulmonary sulcus are most often malignant (so-called Pancoast tumors). Masses at the extreme periphery of the lung are often found to arise from the chest wall and less frequently from the pleura. In either instance, malignancy is not uncommon. The lack of a precise definition for the term coin lesion and the selectivity of the material in the different series accounts for the wide variations in the incidence of cancer in the cases which have been recorded.

TABLE II.—PATHOLOGIC DIAGNOSIS

	No. cases	Per cent
Alveolar cell (terminal bronchiolar) carcinoma	3	7.5
Adenocarcinoma arising in a bronchial adenoma	1	2.5
Metastatic adenocarcinoma, thyroid	1	2.5
Metastatic adenocarcinoma, prostate	1	2.5
Metastatic adenocarcinoma, salivary gland	1	2.5
Bronchogenic carcinoma in situ and tuberculoma	1*	2.5
Tuberculoma	28	70.0
Hamartoma	2	5.0
Xanthogranuloma	1	2.5
Coccidioma	1	2.5

*This case has not been included in our statistics among the patients with coin lesions showing malignancy. It is true that the patient had a bronchogenic carcinoma in situ, but this was an additional finding. The coin lesion itself was benign (tuberculoma). Case reported in detail elsewhere (15).

Accurate comparison of data in the various reported series is unfortunately not possible, for not all of the important facts concerning each lesion are clearly stated in the reports. Nevertheless, in no reported series has the incidence of cancer been insignificant and most authors advocate prompt excision of these lesions. The degree of assurance afforded by the presence of calcium within the mass is debatable. Some observers believe that it offers strong presumptive evidence of benignancy and have advised observation of those patients whose lesions show calcification. Contrary opinions have been expressed and we are among those who believe that the amount of security offered by calcification within a coin lesion is relative rather than absolute. It is believed that the roentgenographic visualization of calcium within a peripheral nodule is not sufficient reason to withhold from the patient the potential benefits that may be derived from its histologic examination.

DISCUSSION

The average age of the 40 patients in this series was 33 years; the oldest was 70 and the youngest 19 years of age. The majority of these patients were young, apparently healthy, adult males on active duty in the Armed Forces. In each instance, the lesion represented an accidental discovery on routine x-ray examination of the chest, for none of the patients had pulmonary symptoms. The histo-

Fig. 1.

logic diagnoses of the lesions in this series are tabulated in Table II.

The incidence of cancer in this series was 17.5 per cent. Twenty-eight or 70 per cent of the lesions were classed as "tuberculomas." It is noteworthy that in the majority of patients in this series, this term could be applied only in a general rather than a specific sense, for only exceptionally was it possible to establish unequivocally the tuberculous nature of these nodules by the demonstration of tubercle bacilli by Ziehl-Neelsen stained smears. Even less often could tubercle bacilli be cultured from them. As a matter of fact, the pathologist most frequently reported them as "chronic fibrocaseous pulmonary granuloma, compatible with a tuberculous origin." It is entirely possible that at least some of these lesions may have represented histoplasmosis, coccidioidomycosis, or other of the deep fungi. Other roentgenographically identical lesions were found, on sectioning, to be blocked tuberculous cavities. Unfortunately, it is impossible to differentiate by roentgenographic examination the so-called "mature tuberculoma" from a lesion which is actually a blocked cavity, perhaps containing amorphus calcium and laden with myriads of virulent tubercle bacilli. Three (10.3 per cent) of the tuberculomas in this series fell into that category. It is well established that tuberculomas may enlarge, even after a prolonged quiescent period. The danger of breakdown with cavitation and bronchogenic dissemination of presumed tuberculomas which are in reality blocked cavities can scarcely be minimized. Grenville-Mathers reported 22 lesions, considered to be tuberculomas, which were followed roentgenographically. Cavitation and spread occurred in 3 instances (13 per cent).

DISTRIBUTION

The distribution of coin lesions of the lung was as follows: right upper lobe in 11 cases, right middle lobe, in 2, right lower lobe in 9, right middle and lower lobe, in 1, left upper lobe, in 5, and left lower lobe, in 12 cases. A fairly even distribution among the 5 lobes is observed, so that it may be said that coin lesions have no characteristic location. With reference to the lesions diagnosed as tuberculomas, it is worthy of mention that they did not show a remarkable tendency to occupy those sites for which tuberculous lesions commonly show a predilection: namely, the apical and posterior segments of the upper lobes and the superior segments of the lower lobes. On the contrary, they were distributed throughout the various bronchopulmonary segments with approximately equal frequency. Does this indicate that a tuberculous focus in an unusual location is more likely to assume the form of a tuberculoma than one situated in a more common site? Following are brief abstracts of the case histories of 5 patients with coin lesions of the lung. They exemplify certain pertinent and important points in connection with these peripheral pulmonary nodules.

CASE 1. J. J. McC., a 37 year old white male, was hospitalized because of a round, circumscribed, smoothly outlined, homogeneous nodule in the anterior segment of the left upper lobe (Fig. 1) which was discovered in a routine chest roentgenogram. The patient had no complaints. Bronchoscopy revealed a normal tracheobronchial tree. The sputum was negative on smear for acid-fast bacilli. The tuberculin skin test was positive in the first strength. Removal of the lesion was elected. At thoracotomy a firm, but not hard, lesion measuring about 2.5 centimeters in diameter was palpated in the upper lobe.

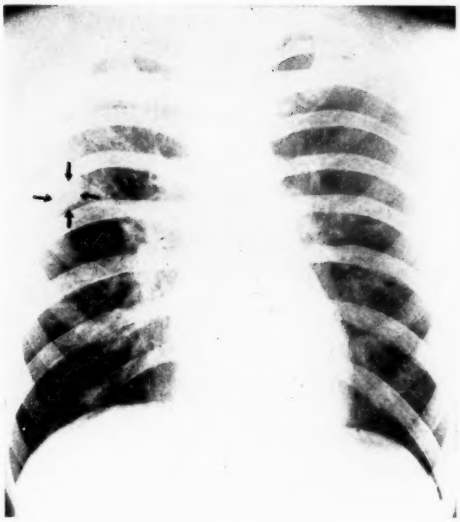

Fig. 2.

Fig. 3.

It was removed by local enucleation technique. The specimen was cut at the table. The cut section showed a pink homogeneous mass which presented a picture unlike that of a tuberculoma. Immediate frozen sections were obtained. Histologic examination showed the typical features of bronchiolar ("alveolar cell") carcinoma. A left upper lobe lobectomy and hilar node dissection was promptly done. Study of the paraffin sections confirmed the diagnosis. No malignancy was found in the remainder of the lobe. All hilar nodes were negative. After an appropriate period of postoperative convalescence the patient was returned to full duty in the Navy. At the time of his latest follow-up, more than 3 years after resection, he remained free of symptoms and his chest roentgenograms were negative.

The indication for surgery in this patient was the presence of a small space-occupying lesion of undetermined etiology. Prompt surgical intervention permitted removal of a malignant tumor by conservative pulmonary resection, possibly before metastases had occurred.

CASE 2. J.N.H., a 24 year old white male, was hospitalized 16 months after a round, sharply marginated mass of homogeneous density, measuring 2 centimeters in diameter, was discovered in the right midlung field. When it was first noted the mass was considered unimportant and no treatment was advised. Upon the patient's entry into the Naval service the lesion was noted on his enlistment chest roentgenogram (Fig. 2) and he was hospitalized for study and treatment. The mass had not changed appreciably in size in the intervening 16 months and the patient had no symptoms. Intensive studies were carried out to determine the nature of the lesion, but all diagnostic efforts were unrewarding. Smears and cultures of the sputum were negative for mycobacterium tuberculosis. The tuberculin skin test was negative in the first strength and slightly positive in the second dilution. Bronchoscopy was negative. The pulmonary lesion, as demonstrated by serial chest roentgenograms, remained stable until about 2½ months after admission, when a spread occurred. The initial spread was localized in the region of the primary lesion. It was felt that the patient had a tuberculoma which had broken down and disseminated. Later the patient developed extensive small nodular infiltrations in all lobes of both lungs (Fig. 3). This was interpreted as miliary spread of tuberculosis and that diagnosis was made on clinical grounds without bacteriologic confirmation. Streptomycin and para-aminosalicylic acid were given but the lesion continued to progress. The patient developed a pericardial effusion and pericardiocentesis was performed on 2 occasions. A total of 1,300 cubic centimeters of bloody fluid was obtained. Papanicolaou stains of this fluid showed malignant cells. A lung biopsy of the right middle lobe was then done. It showed bronchiolar ("alveolar cell") carcinoma. The operation was well tolerated but the patient's postoperative course continued to be progressively downhill and he died with signs of widespread metastases approximately 6 months after his admission and 22 months following discovery of the lesion.

Fig. 4.

Postmortem examination showed bronchiolar carcinoma involving all lobes of both lungs with metastases to the hilar and mediastinal nodes, the right pleura, pericardium, heart, liver, kidneys, adrenals, the third and tenth thoracic and the first and fifth lumbar vertebrae, and the left sixth rib.

The roentgenographic appearance of the primary lesion in this patient was almost identical with that seen in Case 1. There was nothing characteristic about the mass that would suggest the diagnosis. This lesion occurred in a young man. It was demonstrated to have remained stable for at least 19 months. In contrast to Case 1, time-consuming diagnostic studies were undertaken and during this interval widespread metastases occurred. Prompt thoracotomy might have permitted removal of this tumor before it metastasized. The disastrous consequences of prolonged delay in instituting definitive therapy are apparent.

Case 3. D.J.F., a 34 year old white male, was admitted to the hospital because a routine chest roentgenogram showed a discrete round lesion measuring 2 centimeters in diameter situated in the left lower lobe (Fig. 4). The patient had no symptoms. Physical examination showed no abnormalities. Bronchoscopy was negative. The bronchial aspirate revealed no acid-fast bacilli on smear. Cultures were planted. The tuberculin skin test was mildly positive in the second dilution. Overpenetrated chest roentgenograms showed faint calcification within the lesion. Left thoracotomy was performed and the mass was removed by local enucleation. When it was sectioned at the table, its gross appearance was characteristic of a mature tuberculoma. The concentric layering typical of that lesion was clearly evident (Fig. 5). No tubercle bacilli were demonstrated on smear and culture of the specimen. The patient's postoperative course was uncomplicated and he was returned to full duty after a suitable period of convalescence.

Fig. 5.

The gross appearance and bacteriologic studies of this lesion indicated that it presented no particular hazard to the patient. This could not be foretold, however, prior to thoracotomy. Compare with Case 4.

Case 4. J.H.McC., a 29 year old white male, was found to have a small round lesion in the right lower lung field when a routine chest roentgenogram was made at the time of a re-enlistment physical examination (Fig. 6). The mass was sharply circumscribed and of homogeneous density except for small specks of calcium in the central portion. A chest roentgenogram made at the same hospital 1 year previously was negative. He was completely free of symptoms. Physical examination revealed no abnormal findings. Bronchoscopy showed a normal tracheobronchial tree. The bronchial aspirate was negative for acid-fast bacilli on smear. Cultures were planted. The tuberculin skin test was positive in the first strength. All other special studies were negative. Right thoracotomy was performed and the lesion was removed by local enucleation from the lateral basal segment of the right lower lobe. The preoperative diagnosis had been tuberculoma. When cut at the table, the specimen showed the gross characteristics of a blocked cavity. The wall was moderately thick and the center showed caseation necrosis with thick grayish-yellow pus (Fig. 7). Bacteriologic examination showed innumerable acid-fast bacilli morphologically typical of Micrococcus tuberculosis.

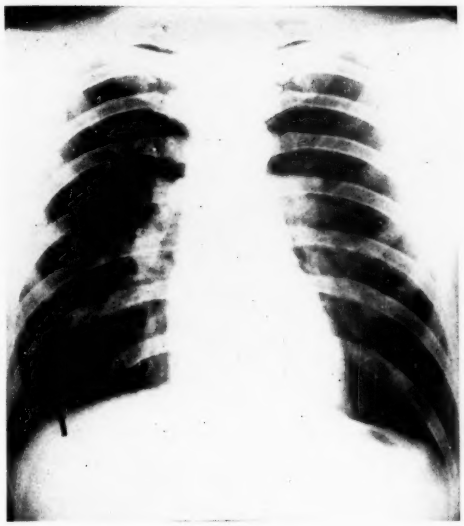

Fig. 6.

This lesion was almost identical with that in Case 3 except that it lay in the opposite lung and was slightly smaller. In contrast, however, this focus was a potentially dangerous one, for only reopening of the blocked bronchus was necessary to permit the discharge of countless tubercle bacilli. There was nothing in the history, the physical findings, or in the roentgenographic appearance to suggest that it differed in any important respect from the lesion in Case 3.

CASE 5.[1] D.L.N., a 32 year old white male, was first hospitalized for study in 1945 following a routine chest roentgenogram which showed a rounded, circumscribed, homogeneous lesion in the right upper lung field (Fig. 8). He had no symptoms and showed nothing abnormal on physical examination. Several sputum cultures were negative for tubercle bacilli and all other special examination showed normal findings. He was returned to full duty in the Navy after 4 months' observation. It was believed that the lesion was a tuberculoma. Follow-up chest roentgenograms were taken at intervals of 6 months throughout 1946, 1947, 1948, 1949, 1950, and 1951. No striking change was noted in the appearance of the lesion until July 1951, when marked enlargement was seen to have occurred (Fig. 9). The mass was no longer homogeneous. Several radiolucent areas suggested cavitation and tomography demonstrated the presence of calcium within the

[1]This case has been reported in detail elsewhere (14).

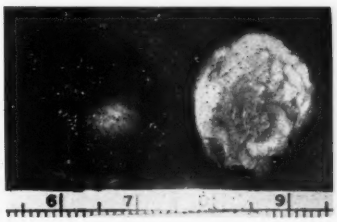

Fig. 7.

mass. It was the opinion that the lesion represented a tuberculoma which had remained quiescent for over 6 years, only to undergo central necrosis with breakdown and excavation. At right thoracotomy the mass, which lay in the posterior segment of the right upper lobe, was removed by segmental resection. When it was opened at the table it was obvious that the lesion did not represent a chronic pulmonary granuloma. The gross appearance strongly suggested tumor. Immediate examination of frozen sections showed well differentiated adenocarcinoma. Subsequent study of paraffin sections showed that the carcinoma had developed in a peripheral bronchial adenoma. A right upper lobe lobectomy was performed. The patient's postoperative course was uncomplicated. He was returned to full duty and remains clinically well with negative chest roentgenograms 1 year after resection.

This case illustrates the futility and the danger of watching space-occupying pulmonary lesions of undetermined etiology. Six years of relative stability did not prove this to be a benign mass nor did the presence of calcium establish the diagnosis of a chronic granuloma.

DIAGNOSIS

It may be stated categorically that in a vast percentage of these lesions, an accurate histologic diagnosis can be made only after the pathologist has had an opportunity to subject the excised specimen to microscopic scrutiny. This implies that an overwhelming majority of diagnostic endeavors which may be undertaken will prove to be fruitless. Such indeed is the case. The lesion having been discovered by x-ray examination of the chest, we believe that each patient with such a mass should have a posteroanterior stereoscopic and appropriate lateral chest roentgenogram. This permits precise localization of the lesion. Occasionally, a Potter-Bucky grid film is helpful in localizing the mass in the lateral view. Tomo-

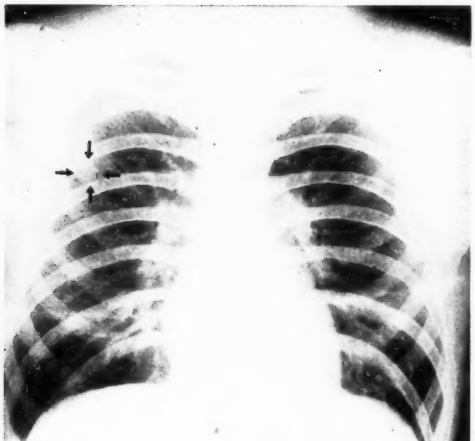

Fig. 8.

grams cut at appropriate levels will delineate the mass nicely and demonstrate calcium well, but generally offer no vital information not provided by the standard films. Although it is almost invariably negative because of the peripheral location of these lesions, bronchoscopy should be done routinely. It is reassuring to rule out the presence of a mucosal lesion involving the larger bronchi. In an exceptional case tuberculous endobronchial disease contraindicating immediate surgery may be encountered. A bronchial aspirate collected at the time should be cultured for acid-fast bacilli and studied cytologically by the Papanicolaou method for malignant cells. The sputum concentrate must be searched for tubercle bacilli on acid-fast stained smears. Sputum cultures should be planted, but delaying surgical treatment for 6 to 12 weeks while awaiting culture reports is not justified. Subsequent reports of a positive culture would be of value in planning the postoperative management of the individual patient. In accordance with our present philosophy concerning the preferred management of patients with small circumscribed tuberculous foci, excisional surgery is the treatment of choice in these patients whether the sputum is positive or negative. The trend toward widespread adoption of this therapeutic regimen appears to be growing. Skin tests for tuberculosis, histoplasmosis, and coccidioidomycosis are carried out in all patients. The results are of some interest but of no practical value in the individual case. Such special examinations as barium enema, gastrointestinal series, and retrograde or intravenous pyelograms do not appear to be indicated in the absence of symptoms or physical findings that would suggest that the pulmonary lesion might be metastatic from the gastrointestinal or urinary tract. There seems little justification for running the gamut of all possible diagnostic undertakings when many of them offer such scant prospects of reward. Furthermore, they are time-consuming, expensive, and usually result only in needless delay in the institution of definitive treatment.

TREATMENT

Spontaneous resolution of these nodules cannot be anticipated. If of tuberculous origin, as they often are, they will not respond to medical treatment. These lesions are not influenced by streptomycin. Mahon and Forsee concluded, from assay studies in 5 patients, that the drug does not penetrate the fibrous wall of tuberculomas. Although it cannot be stated with statistical accuracy just how frequently these lesions cavitate and spread, it is well known that such a disaster occurs occasionally. To attempt to predict the behavior of the individual lesion is nothing but a guess. Even years of known stability do not offer certain security for the future. The hazard presented by a tuberculoma, though probably quite small, is very real. Of much greater importance in the management of coin lesions, however, is the fact that, until histologic study of the excised mass has been carried out, the diagnosis can only be presumptive. Experience has clearly shown that it is unsafe to manage these patients on the assumption that a coin lesion is probably benign. In the series which we have collected, including the patients reported in this paper, malignant neoplastic disease was encountered 108 times in 362 patients in whom the diagnosis was proved histologically. A cancer rate of 29.8 per cent

in these innocent-appearing masses makes it difficult to defend any therapeutic regimen which does not provide for their prompt removal. There is, of course, a calculated risk connected with the extirpation of these small circumscribed lesions. In capable hands, however, this risk is small. There were only 2 deaths among the 362 patients in the series which we have reviewed, a mortality rate of 0.55 per cent. This compares favorably with that encountered with appendectomy or hernioplasty in a good surgical environment. The mortality in at least 1 case could not be attributed to the treatment of coin lesion. A thin-walled aneurysm, erroneously diagnosed as a peripheral pulmonary mass, was ruptured at the time of surgery with a fatal outcome. A trial of irradiation has no place in the management of these obscure peripheral pulmonary nodules. A grave burden is assumed by one who advises expectant observation of these lesions, for a differential diagnosis cannot be made on the basis of their growth characteristics. Benign lesions may and often do grow. Blocked tuberculous cavities may lie dormant for long periods, but the draining bronchus may open at some future time with a resultant spread of the disease. Malignant tumors may remain relatively stationary for months or years only to disseminate with explosive suddenness at a later date (Case 2). In this series, the treatment of the patients consisted of: lobectomy in 3 instances, segmental resection in 2, wedge resection in 6, local enucleation in 26, lung biopsy in 1, rib biopsy in 1, and wedge resection and lobectomy in 1.

We do not propose to offer a detailed discussion of the technical aspects of the removal of these lesions. When the chest has been opened, the method one chooses to employ in the extirpation of the mass is a matter of surgical judgment. If the findings on inspection and palpation offer strong presumptive evidence that the lesion is a tuberculoma, we commonly excise it by the local enucleation technique. Occasionally, if it is situated near the free margin of a lobe, we employ wedge resection. If the characteristics of the mass arouse the slightest suspicion of cancer, the bronchopulmonary segment in which it lies is removed by segmental resection. In all cases the mass is

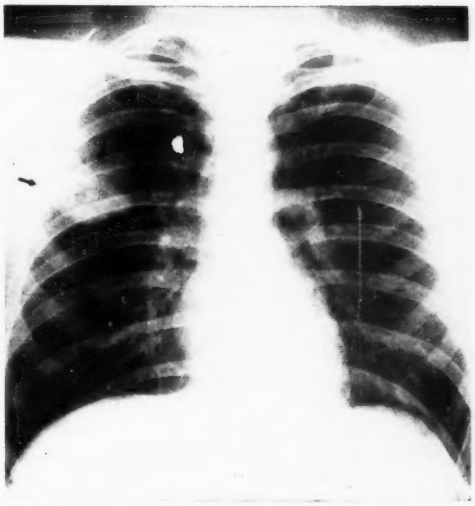

Fig. 9.

sectioned at the table. One can never be certain of the precise nature of these lesions, even when the excised mass is in the hand. If the diagnosis is not obvious from gross inspection, immediate frozen sections are made and histologic examination is carried out. If a primary malignant lesion is found, the extent of further excisional surgery will depend upon circumstances of the particular case and the philosophy and convictions of the responsible surgeon. It is not within the province of this paper to discuss the relative merits of radical pneumonectomy and simple lobectomy in the surgical management of small localized peripherally placed cancers of the lung.

SUMMARY AND CONCLUSIONS

The problem presented by small, solitary, circumscribed, asymptomatic peripheral pulmonary nodules has been discussed. A definition of the term coin lesion has been proposed, and a series of 40 patients with masses of this type has been reported. The nodule in each case was discovered upon routine x-ray examination of the chest. In all except 2 of the cases herein recorded the mass was managed by surgical excision. Tuberculoma was the usual preoperative diagnosis. A malignant tumor was encountered in 7 instances (17.5

per cent). There was no surgical mortality and the postoperative morbidity was minimal. A spread did not occur in any of the patients whose lesion proved to be of tuberculous origin. Five case summaries have been presented in some detail to illustrate the hazards of the watchful waiting program sometimes advocated in cases of this type. Unwarranted reliance on indirect and intuitive diagnostic criteria based on the characteristics of the roentgen shadow, such as calcification and nonenlargement of the lesion, can only serve to deprive the patient of the advantages of early roentgenographic detection. Timely histologic identification is thus not obtained and he is denied the benefits of prompt surgical, antibiotic, and chemical therapy. Our own experience and that reported by others has convinced us that surgical excision without undue delay is the treatment of choice in patients with coin lesions of the lung.

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CANCER OF THE RECTUM

Results of Treatment of All Cases Admitted to the Pondville Hospital June 1927 Through December 1946

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WHEN the Pondville Hospital was first opened by the Massachusetts Department of Public Health in June 1927, the first patient admitted to the hospital was suffering with cancer of the rectum. During the interval between that date and December 31, 1946, 796 patients with cancer of the rectum have been admitted to the general clinic. Ninety-four per cent of these, or 749, have been admitted to the hospital for study, treatment, and, in many instances, for terminal care. This represents 5.7 per cent of the 14,013 cases of cancer observed during the period of approximately 20 years.

Six hundred and ninety (86.6 per cent) were primary cases. Eighty-seven (12.6 per cent) of these had had a colostomy performed before admission. Of the latter group, 8 were subjected to radical surgery at this hospital.

During the early years of this report, the Pondville Hospital admitted many patients in the terminal stages of cancer, but in the later years only treatable patients were admitted. When these cases are grouped according to the American College of Surgeons' classification, we find that in each successive 5 year period there has been an increasing percentage of 1 A, limited to bowel wall, and 1 B, local extension with mobile tumor, cases. These are the most favorable cases for cure.

DATA

This series comprised 544 males (68.3 per cent) and 252 females (31.6 per cent). This is the usual ratio reported in other series. The age of the patients ranged from 19 to 97 years. Six per cent were less than 40 years of age. The median age was in the 60 to 64 year group (Table I).

There were 43 cases (5.4 per cent) of multiple malignant tumors in this series. Forty-two patients had a second cancer, 1 had 3, and 1 a fourth.

Heredity does not seem to play an important part in this disease. A few had a parent who had had cancer of the rectum. Twenty-nine had a sibling who had the same disease, but we do not know how many siblings these patients had (Table II).

Bleeding was the most common symptom. Rectal pain and tenesmus occurred when the lesion was near the sphincter. There was a group of patients whose only symptoms were a change in bowel habit (Table III).

The following classification of cases according to the clinical findings was adopted several years ago by the American College of Surgeons:

AMERICAN COLLEGE OF SURGEONS' CLINICAL CLASSIFICATION

A. Tumor limited to the bowel wall
B. Local extension but mobile tumor
C. Local extension with fixed tumor
D. Regional metastases
E. Hepatic metastases
F. General abdominal metastases

Cases classified under A, B, and D are the only ones suitable for an attempt at cure. In some of the other groups, palliative procedures may be carried out.

During the early years of the study, the totals of the A and B groups, the operable cases, were as low as 12 per cent of the total primary cases, but during the last years the

Reported according to the method approved by the Joint Committee on Reporting Cancer End Results of the American College of Surgeons, American College of Radiology, College of American Pathologists, and the American Cancer Society, Inc.
From the Pondville Hospital, Massachusetts Department of Public Health, Walpole, Massachusetts.
This is publication No. 163 of the Pondville Hospital.

TABLE I.—AGE OF PATIENTS

Age group years	No. patients
Under 34	29
35–39	23
40–44	36
45–49	63
50–54	87
55–59	107
60–64	143
65–69	111
70–74	109
75–79	59
80 and over	29
Total	796

percentage was about 33. Approximately 25 per cent of the patients with primary cases had liver metastases when examined at operation.

DURATION OF SYMPTOMS COMPARED WITH THE EXTENT OF THE DISEASE

The median duration from the patient's first symptom to treatment was determined to be between 6 and 8 months in all stages except C, and in that group it was 9 to 11 months. In the group D cases of patients with regional metastases, the E cases with hepatic metastases, and the F cases with general abdominal metastases, the mean duration was no greater than in some of the favorable cases placed in groups A and B (Table IV).

This means that one patient might delay treatment several months and still be in the operable group, while in another patient, in the same interval, the disease might become inoperable. There are different types and grades of malignant tumors, some of them showing metastases earlier than others.

The location of the tumor in the rectum may have some bearing upon the time at which symptoms first occurred. For instance, a low lesion approaching the sphincter may produce earlier symptoms than the tumor in the ampulla, and, therefore, it may be a smaller and more curable lesion when it is first noticed.

Because of so many factors, it is not possible to guarantee that there will always be a direct ratio between the earliness of treatment and the probability of cure.

TABLE II.—HEREDITY

	No.	Per cent
Family history of cancer		
None	548	
1 parent	53	6.7
1 sibling	42	5.3
Family history of cancer of the rectum		
None	610	
1 parent	5	0.6
1 sibling	29	3.6

Not all patients were questioned.

TABLE III.—SYMPTOMS

	No.	Per cent
Bleeding	591	74.2
Rectal pain and tenesmus	248	31.1
Frequent stools	212	26.6
Constipation	205	25.7
Change in bowel habit	122	15.3
Loss of weight	83	
Abdominal pain	71	
Hemorrhoids	30	
Mass or lump	19	
Obstruction	17	

Some patients had more than 1 symptom.

RESECTABILITY

The resectability rates have been determined in various periods. During the early years nearly all of the patients admitted had advanced cancer. Gradually the proportions who could be submitted to a radical removal of the rectum have increased. In Table V the resections include those done for palliation as well as those in whom cure seemed possible.

OPERATIVE MORTALITY

Deaths within 30 days or while the patient was in the hospital have been considered operative deaths. The early operative mortality

TABLE IV.—DURATION OF SYMPTOMS IN MONTHS

Duration, months	American College of Surgeons' Classification						Totals
	A	B	C	D	E	F	
Less than 1		1	1	1		1	4
1	8	3	9	5	4	2	31
2	4	3	12	12	8	3	42
3	3	8	6	10	8	2	37
4–5	10	12	22	27	12	5	88
6–8	20	15	26	31	17	8	117
9–11	5	5	15	14	5	6	50
12–17	12	13	30	18	9	5	87
18–23	5	2	7	5	3	1	23
24–47	6	9	31	13	11	5	75
48+	1	1	2	4			8

TABLE V.—RESECTABILITY RATES IN CANCER OF RECTUM, 1928 TO 1946

Years	No. admitted to hospital	No. receiving resections	Per cent
1928–1931	120	10	8.3
1932–1935	175	41	23.4
1936–1939	207	90	43.4
1940–1943	153	86†	56.2
1944–1946*	64	36	56.2
Totals	719	263	

*3 year period.
†Includes 3 secondary cases.

in this series was very high. With the greater experience with the operation, the better use of fluids including blood, and the use of sulfonamides and antibiotics, the operative mortality has been steadily reduced. The rate for the last 3 years of this study was 8.3 per cent (Table VI).

It is to be noted that, while the resectability rate has constantly increased and a larger percentage of the elderly and poor risk patients have been operated upon, still the operative mortality has constantly gone down.

HISTOLOGY

Of 651 pathologic examinations in these cases, adenocarcinoma was reported in 503 instances (77 per cent). There were 101 cases of malignant adenoma, 19 of carcinoma simplex, and 14 of carcinoma of the colloid type. Blood vessel invasion was noted microscopically in 81 cases.

TABLE VI.—OPERATIVE MORTALITY

Radical Resections

Years	No. of operations	No. of deaths	Per cent
1928–1931	10	8	*
1932–1935	41	19	46.3
1936–1939	90	28	31.1
1940–1943	86	10	11.6
1944–1946†	36	3	8.3

Exploratory Laparotomies and/or Colostomies

1928–1931	29	10	34.4
1932–1935	61	10	16.4
1936–1939	65	19	29.3
1940–1943	38	2	5.2
1944–1946	18	1	0.5

*Too few cases to give a percentage figure.
†3 year period.

TABLE VII.—POSITION AND SIZE OF LESION IN RADICAL OPERATIVE GROUP

Distance of lesions from anus, cm.	No. of cases	Per cent
Within 5	143	58.1 } 87.3% within reach of
5 to 10	72	29.2 } examination finger.
10 to 15	24	9.7
15+	7	2.8
Total	246	
Diameter of lesion, cm.		
Up to 5	140	56.9
5 to 10	103	41.8
10 to 15	3	1.2
Total	246	

POSITION AND SIZE OF LESION

In Table VII it is to be noted that over 87 per cent of the lesions were within 10 centi-

TABLE VIII.—TREATMENT IN CARCINOMA OF RECTUM

Primary Cases

Resections	No. cases
Abdominoperineal resection (Miles)	207
Abdominoperineal resection (Lahey)	8
Abdominoperineal resection (Jones)	3
Colostomy and posterior resection	38
Colostomy and anterior resection	3
Abdominal resection with anastomosis	1
	260
Palliative	
Exploratory laparotomy only or with colostomy	208
Electrocoagulation	6
Radiation (x-ray and/or radium)	53
Colostomy and radium	1
	268
Total cases treated	528

Secondary Cases

Resections	
Abdominoperineal resection (Miles)	1
Colostomy and posterior excision	1
Posterior resection	1
	3
Palliative	
Exploratory laparotomy and colostomy	7
Electrocoagulation	1
Radiation	46
	54
Total cases treated	57

TABLE IX.—A REPORT OF 5 YEAR END RESULTS IN CANCER OF RECTUM

This series consists of all patients with cancer of the rectum both early and advanced applying to Pondville Hospital during the period 1927 to 1946.

General Summary		No. of cases
Total experience—All patients applying		796
Section A	Cases not previously treated	681
Section B	Cases previously treated	97
Other	a. Applied after treatment elsewhere, no evidence of cancer on admission or thereafter	9
	b. Consultation only, no treatment requested	9

Section A. Cases not previously treated					Section B. Cases previously treated				
Results at end of 5 years		No. of cases			Result at end of 5 years		No. of cases		
		With microscopic proof	Without microscopic proof	Total			With microscopic proof	Without microscopic proof	Total
Group I	c. Refused proffered treatment	21	22	43	Group I	c. Refused proffered treatment	—	—	—
	d. Untraced for full 5 years without recurrence at last examination	—	—	—		d. Untraced for full 5 years without recurrence at last examination	—	—	—
Group II	e. Dead within 5 years of other causes without recurrence of cancer	13	—	13	Group II	e. Dead within 5 years of other causes without recurrence of cancer	1	—	1
Group III	f. Dead, cancer present or died of complications of treatment	438	93	531	Group III	f. Dead, cancer present or died of complications of treatment	67	14	81
	g. Dead—presence of cancer unknown	12	—	12		g. Dead—presence of cancer unknown	2	1	3
	h. Living with cancer present at 5 years	8	—	8		h. Living with cancer present at 5 years	6	1	7
	i. Living with condition unknown at 5 years	2	—	2		i. Living with condition unknown at 5 years	2	1	3
	j. Untraced full 5 years with cancer at last examination	—	—	—		j. Untraced full 5 years with cancer at last examination	—	—	—
	k. Untraced full 5 years, not classifiable in "d" or "j"	—	—	—		k. Untraced full 5 years, not classifiable in "d" or "j"	—	—	—
Group IV	l. Living, continuously free of cancer, verified by medical examination at 5 years	63	—	63	Group IV	l. Living, continuously free of cancer, verified by medical examination at 5 years	—	—	—
	m. Living, apparently free of cancer, not verified by medical examination at 5 years	8	—	8		m. Living, apparently free of cancer, not verified by medical examination at 5 years	2	—	2
	n. Living, successfully treated for recurrence, free of cancer at 5 years	1	—	1		n. Living, successfully treated for recurrence, free of cancer at 5 years	—	—	—
Total		566	115	681	Total		80	17	97

meters from the anus. All of these cancers, as well as some of those 10 to 15 centimeters up the rectum, could be felt by the examining finger. All of the other lesions were within reach of the sigmoidoscope.

Here it might be well to stress our rule for the examination of all rectal cases. The order is: (1) digital examination, (2) sigmoidoscopy and biopsy if a lesion is seen, and (3) barium enema only if the other examinations are negative. A barium enema, in the presence of a partially obstructing lesion, may cause the obstruction to be complete and not add anything to our knowledge of the case.

In more than one-half of the operative cases the lesion was less than 5 centimeters in size (Table VII).

TREATMENT

Two hundred and sixty cases in the primary group were considered resectable. Ten per cent of these patients were found at operation to have metastases in the liver or elsewhere

TABLE X.—ANALYSIS OF RESULTS IN RADICAL OPERATIVE GROUPS

Sex	No. of cases	5 year survivals		5 year cures*	
		No.	Per cent	No.	Per cent
Male	174	50	28.4	36	20.4
Female	86	29	33.7	26	32.3
Totals	260	79		62	
Age, years					
0–44	24	7	29	5	20
45–49	16	5	31	5	31
50–54	26	10	38	9	34
55–59	39	14	30	11	38
60–64	52	14	26	10	19
65–69	48	16	29	12	25
70+	55	13	25	10	18
Totals	260	79		62	
Duration of symptoms, months					
0–3.9	54	14	25.9	14	25.9
4–8.9	98	38	38.7	30	30.6
9+	99	26	26.2	17	17.1
Unknown	9	1		1	
Totals	260	79		62	
Stage of disease					
A	60	26	43.3	24	40
B	57	23	40	19	33
C	34	9	26	5	14
D	84	21	25	14	16
E-F	25	0		0	
Totals	260	79		62	

*Patients well 5 years and checked by a physician.

that could not be removed, or the local invasion was such that the operator could not expect cure. It was always the policy to carry out the resection, if this were possible, in order to rid the patient of troublesome symptoms.

Our usual operation is the Miles abdominoperineal resection, and this was carried out in 80 per cent of the cases. During the early years there were 11 two stage (Lahey or Jones) operations performed. Thirty-eight patients had a colostomy and posterior resection, usually in two stages. This was a safer operation for some of the elderly patients, although not as radical a removal of the tumor as in the Miles procedure (Table VIII).

TABLE XI.—ANALYSIS OF 5 YEAR CURES BY SEX AND DURATION OF SYMPTOMS IN STAGE A PRIMARY CASES TREATED BY RADIOLOGY OPERATION

Sex	Duration of symptoms, months	No. of cases	No. of 5 year cures
Male	0–8.9	28	12
	9+	10	3
	Unknown	1	0
		39	15
Female	0–8.9	7	5
	9+	11	3
	Unknown	3	1
		21	9
Totals		60	24

RESULTS

The results of treatment of this series are reported according to the method recently approved by the American College of Surgeons, the College of American Pathologists, the American College of Radiology, and the American Cancer Society, Inc. All cases of cancer of the rectum examined in either the clinic or in the hospital have been recorded and accounted for (Table IX).

Of 796 patients suffering from this disease we have final follow-up data on all. Therefore there are no "lost" patients.

Further analysis of results. From Table IX it is possible to determine either the number of 5 year "cures" or 5 year survivals. Five year "cures" are not claimed unless there has been microscopic proof of cancer and unless the patient has been examined by a physician after 5 years have elapsed.

Of 796 patients in this series, only 92 survived for 5 years and 63 were well as confirmed by a medical examination. Ten others were said to be well but had not been examined.

If we exclude those coming for observation after treatment, for consultation only, those refusing treatment or having no pathologic examination, there are only 625 cases available for study. Of these there are 92 survivors, 63 five year cures, and 10 possibly well.

Again, if we consider only primary untreated cases and exclude the same groups, there are 532 cases to study. There are 82 survivors, 63 five year cures, and 8 possibly well.

Of these 532 patients, 260 were subjected to radical operation. There were 79 survivals (30.3 per cent) for 5 years, 62 five year verified cures (23.8 per cent), and 8 (3 per cent) possibly well. Two others with primary cases were well at 5 years, 1 after radium treatment and 1 cured by biopsy excision only.

Of the secondary cases, 3 were subjected to radical surgery and 2 of these were 5 year cures. There were only 10 five year survivals.

In Table X we have considered various factors in relation to the final results. From our data we cannot conclude that there is any definite ratio between the length of symptoms and the chances of cure. Those patients who delayed from 4 to 9 months showed a higher curability than those receiving treatment during the first 3 months after symptoms appeared. This could be explained by the fact that some cancers produce symptoms earlier than others, and hence earlier treatment is given.

The males outnumbered the females in the group operated upon by 2 to 1. However, there was a relatively slightly larger percentage of cures in the females.

When studied according to the stage of the disease, the best results were obtained when the cancer was limited to the bowel wall or was movable. When lymph nodes were involved the results were poorer, but there were some cures.

Analyzed by age groups we can draw few conclusions of value. The groups are small, but the greatest number of cures is in those from 50 to 59 years of age.

In Table XI the stage A operative cases are analyzed according to the duration of symptoms. The group is small, but from these figures there is a definite suggestion that in the women better results were obtained and that those with symptoms of shorter duration fared better than those with longer symptoms.

SUMMARY

1. Data are presented on 796 cases of patients with cancer of the rectum admitted to the Pondville Hospital and Clinic over a 19½ year period.

2. All cases are accounted for in this method of reporting.

3. Data are presented in such a way that 5 year survivals or 5 year cure results may be determined.

4. The results of 260 radical operations for cancer of the rectum are presented.

5. In determining the final results the most important single factor in influencing the cure rate is the stage of the disease at the time of the first examination.

EDITORIAL

SURGERY
Gynecology and Obstetrics

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JULY, 1953

A PROBLEM FOR THE ANESTHETIST AND SURGEON—CARDIAC ARREST

MANY articles have appeared in the past 3 to 4 years concerning cardiac arrest, its causes, prevention, recognition, and the necessity for early active treatment if this dreaded complication arises. Most surgeons know that such a condition may occur, yet have not recognized it, nor would they know how to handle such a problem.

The purpose of this editorial is to encourage each surgical and anesthetic department regardless of size or location to develop together their skills in the prevention, recognition, and treatment of cardiac arrest. Most hospitals do not have an organized experimental laboratory, but one can easily be set up for this important demonstration. Intratracheal intubation of the dog is essential and after the chest is opened positive pressure is maintained by the anesthetist. For demonstration purposes a midline sternal incision is best. The pericardium is opened, completely exposing the heart and region of the great vessels. The anesthetist will now play the important part in the demonstration. Attention is called to the free airway and the bright red color of the blood and the well oxygenated appearance of the cardiac muscle, lungs, and other tissues. Various methods of producing obstruction to the free exchange of oxygen can then be tried showing how easily and rapidly cyanosis and cardiac irregularities develop. When the tracheal catheter is completely occluded, the heart rate speeds up, cyanosis develops, the heart dilates and slows. One marvels that the heart does not rupture, it becomes so distended and cyanotic. If at this time the airway is opened and oxygen is delivered to the lungs and the waste products removed, a dramatic response is seen. The heart receives oxygen and at once it renews its work with great vigor, cyanosis clears, and the heart size returns to normal. The importance of this open airway to the cyanotic, dilated heart that is at the point of arrest has been most beautifully shown. The airway, again, should then be completely closed off allowing at this time the heart to pass through the stages mentioned to a complete arrest. The heart will be markedly dilated, cyanotic, and without contraction. When allowed to stay in this condition ½ to 1 minute, an open airway alone may not be sufficient to resuscitate the heart action. Manual compression of the heart should then be started so that the heart is completely emptied by forcefully compressing the heart and then releasing it, thus allowing the heart to refill. Just as soon as it refills to normal size, rapid vigorous compression should be repeated. Systole and diastole must be continued by

compression and relaxation of the hand or hands so that good color returns to the tissues and a pulse can be felt in the peripheral vessels. The arrest may be overcome in two or three compressions, or a considerable length of time may be required to restore cardiac rhythm.

Careful observation of the cardiac muscle is essential to differentiate between complete cardiac arrest and ventricular fibrillation. The appearance of the fibrillating ventricles has been described in various ways: worm-like motion of the muscles, independent motion of each muscle bundle, so that no function of the ventricles occurs. When ventricular fibrillation is seen, cardiac compression must be instituted until the defibrillator is ready to function. (A defibrillator should be a part of the emergency equipment of each surgical department.)

Ventricular fibrillation may not occur following the experiment described, and in our experience a severe electric shock is usually required to cause the heart to go into ventricular fibrillation. This shock is produced by clamping one electrode to the neck and the other to the groin of the dog and allowing the electric current received from a wall plug to pass through him. Two or three shocks may be necessary in the larger dogs to produce fibrillating ventricular muscles. When this occurs it is easily seen that the heart is not functioning, yet all muscle fibers are in independent motion. There is no pulse, no heart sounds, and only by direct vision or an electrocardiogram can the diagnosis be made and the condition be differentiated from a complete cardiac arrest. The heart distends and becomes very cyanotic and, except for the fibrillating muscle, appears like the heart in complete arrest. Manual compression of the heart is essential for oxygenation of the heart and brain, and when the heart muscle is well oxygenated the defibrillator should then be used. The animal laboratory is the place to acquaint the house and attending staffs with the technique and dangers of this instrument, as well as the realization that it may take time and effort to accomplish defibrillation.

Cardiac resuscitation is only possible if one is able to recognize a cardiac arrest and institute a bold, well organized plan. The animal laboratory is invaluable in this training program, and the lessons learned here may save many lives. Aseptic and careful surgical technique undoubtedly will aid in the recovery of the animal.

The most important lesson to be learned in this demonstration, both for the anesthetist and surgeon, is the realization of the importance of an open airway in the prevention of cardiac arrest.

EGBERT H. FELL.

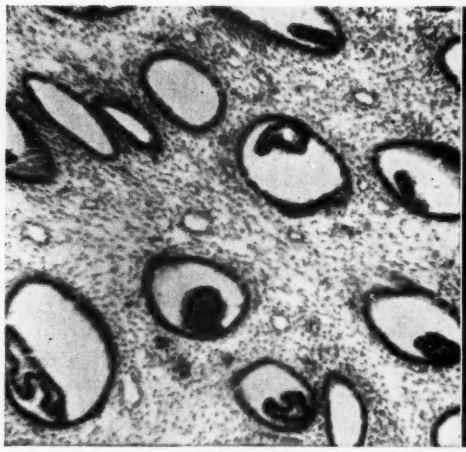

Fig. 2.

Fig. 3.

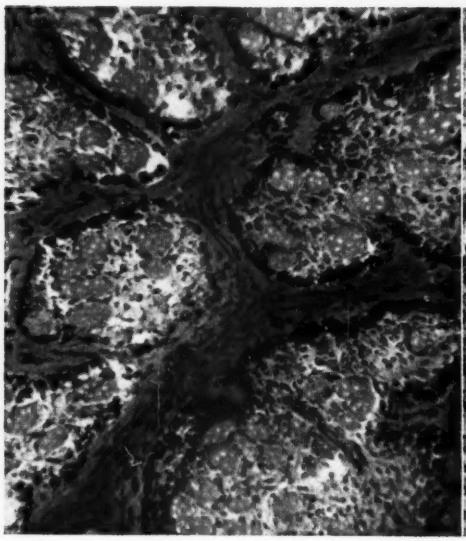

Fig. 4.

Fig. 5.

Rapid Frozen Sections—Technique of Their Preparation and Staining.—Malcolm B. Dockerty.

(Legends on opposite page.)

THE SURGEON AT WORK

RAPID FROZEN SECTIONS—TECHNIQUE OF THEIR PREPARATION AND STAINING

MALCOLM B. DOCKERTY, M.D., Rochester, Minnesota

THE attitude of the busy pathologist responding to a hurried summons from the operating room for purposes of making a "fresh frozen section" is like his attitude toward a court summons—one of distaste. He is asked to render a microscopic diagnosis employing a method with which he is unfamiliar, and using a vital stain quite dissimilar to those to which he is accustomed. Yet, on what he sees through a glass darkly, so to speak, depends a decision which may dictate drastic changes in the operative procedure planned by a temperamental colleague. Decision must be prompt; the diagnosis unequivocal. Small wonder, then, that capable pathologists are wont to discourage requests for fresh frozen sections.

Yet it is axiomatic that proper surgical therapy is chiefly predicated on the establishment of accurate diagnoses and it is equally obvious that in the *best interests of the patient*, the proper time for such diagnosis to be made is at the time of surgical exposure. It is only natural that surgeons who have observed the routine employment of rapid frozen section techniques under ideal conditions are impatient with their brethren in the laboratory over failure of the latter to share enthusiasm in, and to explore, the possibilities of the method. In my opinion, these two opposing attitudes could be brought into harmony by a better understanding of the basic principles involved in the making of good frozen sections.

From the Division of Surgical Pathology, Mayo Clinic.

The method herein to be described in some detail is not presented as being original or superior. With minor variations it has been followed for 40 years in the laboratories of surgical pathology at the Mayo Clinic. In the hands of a technician familiar with its details, it can be expected to achieve the following objectives, namely: (1) rapidity—not more than 60 seconds being required to prepare, cut, mount, and stain a section from the average block of tissue; (2) uniformity and thinness of the sections to a tolerance which permits of their being routinely examined cytologically with the oil immersion objectives of the microscope; (3) universal application to sectioning of practically all solid and semisolid tissues of the body (bone and teeth are exceptions to the rule; endometrium, colonic polyps, cortical brain tissue, and lymph nodes *are not*); (4) elimination of all preliminary treatment of tissue, such as formalin-fixation, boiling, drying, or other dilatory hocus-pocus.

With these advantages in mind and with the experience of having observed alike the good and the bad in fresh frozen tissue techniques throughout the United States and Canada, I decided that the profession would not receive unkindly an article dealing with step-by-step details designed to yield the best and most consistent results by using the method.

THE MICROTOME

Of the various freezing microtomes available the Spencer automatic model has served our purposes to best advantage. Its station relative to

Fig. 2. Endometrium showing early differentiative phase of the menstrual cycle with tufting of the epithelium. Obtaining fresh endometrial sections of this quality is a goal of technical ability which *can* be achieved with practice. Polychrome methylene blue, ×100.

Fig. 3. The cutting of soft brain tissue is said to be difficult. Accomplishment of the task is shown in this fresh section of a grade 3 astrocytoma with tumor giant cells. Glial fibrils and myelineated nerve elements are beautifully differentiated. Polychrome methylene blue, ×1,000.

Fig. 4. Bone, also difficult to handle, is here sectioned thinly enough for photomicrographic purposes. Note pink staining of osteoid trabeculae and palisading of dark-staining osteoblasts. Polychrome methylene blue, ×100.

Fig. 5. Microscopic verification of vein involvement in the spread of carcinoma can be carried out in a matter of minutes by fresh frozen sections. Muscle cells stain brownish red, elastica greenish blue, and young connective tissue of the cancer-bearing thrombus a brilliant pink. Polychrome methylene blue, ×60.

the seated technician should be such that the cutting edge of the blade is not more than 8 inches below eye level. Disregard of this important item is one of the prime causes for poor frozen sections since it hampers accurate visual control over the level of freezing which must be within 1 millimeter or less of the first plane of cutting.

Preliminary experimentation rather than the higher mathematics will best decide the matter of setting the adjustment for thinness of sections. On the average machine, a satisfactory point will be found somewhere between the 8 and 12 micron markings and, once correctly determined, this setting should not be tampered with. The only disadvantage attending this permanent setting is that the microtome blade must be advanced about halfway through its forward arc to disengage the ratchet which operates elevation of the freezing platform. In this latter position of the blade, however, the platform may be readily moved up or down. Incidentally, practicing of this "left-handed" maneuver of rapidly raising and lowering the platform pays excellent dividends in the matter of adjusting the knife-edge to the proper level of freezing.

A good workman rarely blames his mistakes on his tools, but the cutting edge presented by the average freezing microtome is the chief cause for poor frozen sections. The knife blade used for paraffin sections will rarely perform on fresh tissue without a face-lifting operation which adjusts the angle subtended by the cutting surfaces to 30 degrees. Moreover, the upper and lower bevels so created must be between 1 and 2 millimeters wide and of uniform width across both upper and lower faces. The presence of these shelves in some way facilitates the proper shaving of tissue "flakes" and their removal. Accordingly it is sometimes found that new knives with narrow bevels do not perform so well as those which have seen some service. When, as a result of repeated resharpening the aforementioned shelves have become too wide, secondary faces should be ground so that their planes of projection meet at an angle of about 20 degrees. By doing this one may prolong considerably the useful life span of the microtome knife.

For results that are worthy of the name, razor sharpness is a *must* for the business end of the microtome knife. There can be no compromise on this item. The original 30 degree angles may be set by using a mechanical rotor, provided adjustments can be made to secure bevels of uniform width across the faces of the blade. Finishing must be accomplished by stropping which is continued until there are no visible irregularities present when the edge of the knife is examined under 60 magnifications of the microscope. A thin coating of oil should then be applied to prevent oxidation. This coating should be gently wiped off from the *upper surface*[1] just prior to use, and for this purpose the employment of a few drops of ether is most helpful.

It is rarely possible to use the same microtome knife for 2 consecutive days without resharpening in the interval. The isotonic saline solution employed in preparing sections results in some rusting in spite of careful drying of the knife after cutting each group of sections. Water, and even the air of the laboratory, are similarly deleterious. Our attempts to maintain "overnight" edge-keenness by employing the principles of oiling or immersion in alcohol, acetone, and ether have met with singular failure. One halfway measure used has been to "edge in" a second period of active duty on fixed frozen or paraffin sections.

SOLUTIONS

Since neutral polychrome methylene blue is a vital stain it is almost axiomatic that the solutions on the surfaces of which the stained sections are to be floated should be nearly isotonic. The advantages of fulfilling this requirement are obvious in the routine cytologic study of sections by using the oil immersion objective. Solutions for receptacles *1* through *3* in Figure 1 are prepared by adding to 500 cubic centimeters of tap water 4.5 grams of fine table salt. (It will be noted that receptacle *1* is constructed of clear glass and placed on a black-painted strip which contrasts sharply with the gray-white color of the unstained sections as they come off the microtome.) Receptacle *4* is filled with a 5 per cent solution of glucose in distilled water with enough camphor added to discourage the growth of molds. This last is a most excellent medium for removing the final traces of excess stain from the sections preparatory to their mounting. Moreover, since the glucose solution receives only traces of stain from this final "rinse" it requires rather infrequent changing. The saline containers, on the other hand, should be emptied following the preparation of sections from each case.

THE FREEZING UNIT

Liquid carbon-dioxide-containing tanks of larger sizes provide ideal mediums for freezing if

[1]Preservation of the oil film on the *under surface* of the cutting bevel prevents the accumulation of saline solution in this area. An undesirable moistening of the tissue block is thus avoided when the latter is being sectioned.

the precaution is taken to replace them as soon as 60 per cent of the original weight of liquid carbon dioxide has been used up. Attempts made to save a few cents by exhausting a tank of its contents will result in slow freezing of tissue blocks as well as irregularities in the level of freezing. As a rule it is well to discontinue use of the tank as soon as the release of short bursts of carbon dioxide fails to produce whitening of the freezing stage within a matter of three seconds. Copper conduits leading from tank to microtome should be fitted with airtight connections. The petcock should operate without binding.

Grooves on the freezing stage should be from 0.5 to 1.5 millimeters in depth and a new stage-top should be mounted as soon as the old one exhibits smoothing of its surface from wear, since frozen blocks of tissue adhere poorly to such. Attempts to regroove worn stages result in the removal of so much metal that the rigidity of this essential unit is seriously impaired.

Instruments for handling the fresh tissue blocks are few in number and very simple in design. As shown in Figure 1, they consist of an 8 inch length of glass rod 4 millimeters in diameter, an ordinary toothed tissue forceps, and a scalpel which has run its race in the operating room. Useful, but not essential, is a small pair of scissors for the trimming of irregular projections from tissue blocks to facilitate ease of removal of sections therefrom. Glass slides and cover slips should be within easy reach.

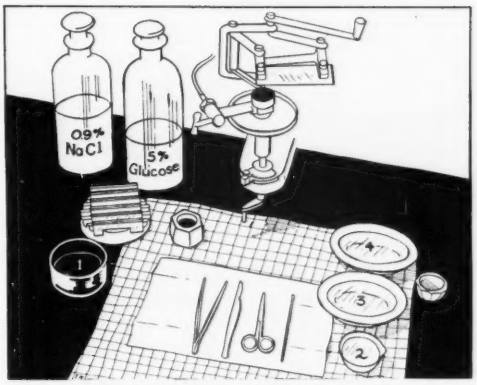

Fig. 1. This sketch shows the essentials of a setup for preparing fresh frozen sections. (See also text for details.)

THE TISSUE

The tissue to be examined must be perfectly fresh. Cytologic detail is distorted in a matter of less than hours by allowing the material to lie around in the laboratory, and for a similar reason, necropsy tissue does not yield very satisfactory preparations.

The size of tissue blocks will vary, and in a subsequent paragraph I shall deal with the handling of the tiny "cores" provided by such instruments as the Silverman needle. When selection from respectable tissue masses is possible, the average block should be rectangular in outline rather than square or round and its dimensions should not exceed 1.5 by 1 centimeter on surface by about 5 millimeters in thickness. Orientation on the freezing stage should be such that the long edge, the mucosal, or the skin surface, is first presented to the microtome knife. Moreover, it is of utmost importance that the cutting edge of the latter engage the tissue at an angle of about 30 degrees if folding of the sections is to be avoided. In all instances save those wherein the tissue is soft and succulent (that is, endometrium, brain tissue, synovia, lymph nodes) the block should be dipped in isotonic saline solution prior to its placement on the freezing stage. Failure to observe this precaution results in separation of the block from the stage during the operation of cutting.

For the actual test run let us suppose that the surgeon has removed a 4 by 2 by 2 centimeter wedge of tissue from the surface of the liver and that the capsular aspect of this wedge contains in its center a whitish nodule which measures 8 millimeters across. From this surgical specimen the pathologist selects a block which centers around the lesion in question. This block, which measures 1.5 by 1 centimeter by 5 millimeters, has the capsular surface of the liver on its longer edge.

The block is gently picked up with the tissue forceps, its lower surface is moistened in saline solution, and it is so placed on the freezing stage that its long axis is oriented in a line connecting the 10 and 4 o'clock positions of the latter. The long capsular edge of the block faces the microtome knife.

In the next step, using the right hand, we bring the blade forward to a position just short of engaging the tissue and simultaneously, with the left, adjust the upper surface of the freezing chamber to a level approximately 3 or 4 millimeters below the plane of the cutting edge. This combined maneuver reduces to a minimum the time consumed in the critically rapid finding of the "frost line" at the end of the freezing phase.

We are now ready to freeze the tissue and this is accomplished with 3 or 4 one second bursts of

Fig. 6. Details of a striated rhabdomyoblast found on fresh frozen section of a polypoid endometrial tumor. This was the only cross-striated cell found in approximately 40 fresh and fixed sections made on the tumor. Polychrome methylene blue, ×950.

carbon dioxide delivered by opening the pinchcock only about one sixth of a turn per burst. The latter should then be turned off completely and approximately 3 seconds allowed to elapse for the level of tissue freezing to reach its maximal height of approximately 3 millimeters. This represents the exact level at which we have adjusted the microtome knife edge and with the right hand we now rapidly advance the knife and separate the unfrozen portion of the block. It is perhaps worth repeating here that by *not* cutting through frozen tissue in this primary step we have completed successfully the most critically important operation in the later securing of satisfactory tissue flakes.

Variation of more than 1 millimeter in the level selected for this preliminary cut spells the difference between success and failure in subsequent steps, because the tissue flake to be selected for staining must be secured on one of the next four sweeps of the knife. If the separation which we have just accomplished occurs through firmly frozen tissue, chipping of the latter will occur. Such chips when mounted and stained exhibit pronounced cellular distortion from rupture of nuclear membranes. If, on the other hand, the frost line has not reached a sufficient height, thawing of the block will ensue before proper sections can be recovered. Refreezing under such circumstances rarely corrects the situation.

The upper surface of the knife having been moistened with a thin film of saline solution, we return the control arm to the neutral position and then rapidly bring it forward. The knife, shaving the surface of the tissue block, removes an almost transparent section which lies on the moistened surface.[1] To remove this flake the palmar surface of the distal phalanx of the right index finger is very lightly applied to the area. One hundred twenty degree flexion of the forefinger, which is kept in gentle contact with the knife, combines with the forces of capillary action to transfer the unfolded section to the finger. Immersing the distal portion of the latter, palmar side up, in saline container *1* and reversing the operation of its removal from the microtome knife readies the floating section for picking up with the glass lifter. Sections 2 and 3 are similarly removed and floated, but by the time we reach the level of sections 4 and 5, the tissue block has begun to thaw and no further sections can be secured without: (1) refreezing the block, (2) raising the freezing table 60 microns (6 "clicks") and finding a new frost line. With small, single biopsies one or both of these maneuvers may be necessary, occasionally, when the pathologist desires to study serial sections. Under normal circumstances, however, it is rec-

[1]Section 1 is frequently unsatisfactory as a result of folding. In such an event it should be quickly wiped off the knife and discarded.

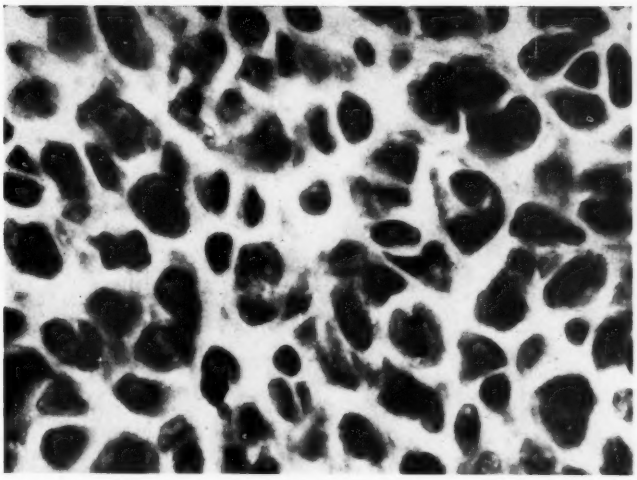

Fig. 7. Nonmelanotic melanoma showing cellular detail and arrangement in alveolar clusters. Polychrome methylene blue, ×1,000.

ommended that failure to secure a satisfactory section from the first four engagements of the knife, as detailed before, should call for "defrosting" of the microtome and repetition of the entire procedure using a new block of tissue. Strict adherence to this rule of self-discipline is guaranteed to produce good sections—sections which are good chiefly *because* they are rapidly made.

STAINING

Grasping the glass lifter as one would a pencil and with its distal end protruding about 6 centimeters beyond the fingertip level, one gently slides it underneath the floating tissue flake which it is desired to stain. In order to avoid folding of the latter, it should be centered on the rod, the end of which should protrude beyond for a distance of about 1 centimeter.

Immersion in the stain is accomplished by holding the lifter at an angle of 45 degrees from the table and steadying the operation by supporting the weight of the hand on the outer surface of the little finger. When the lower end of the lifter is dipped into the stain the section "unwraps" itself, and floats to the surface. With 4 or 5 up-and-down motions of the lifter, performed over a period of 5 seconds, the tissue is raised and lowered from the surface of the stain. This maneuver is necessary to secure satisfactory saturation.

The section now stained and still saddling the glass lifter is transferred to the second (white colored) receptacle. Here it is lowered to the surface of the saline solution, using the lifter as we did in the procedure of staining. Three or 4 "dippings" of the lifter produce considerable bluing of the solution and we now proceed to receptacle 3. Here the last major traces of excess stain are removed, the glucose solution taking care of the final "rinse." When, after refloating the section several times in the glucose, we observe no bluish trails, we are ready for the "miracle" of mounting.

For purposes of clarifying the details of this final step let us take a clean glass slide with an "X" marked on the lower surface, near one end. With the extended right hand in the position of pronation we grasp the slide so that the thumb covers the "X." Holding this position we immerse the distal half of the slide in the glucose at an angle of 45 degrees with the surface and well beyond the floating section. Holding this angle we advance the slide to the point of contact with the section and then simultaneously continue the forward movement while at the same time changing the angle of the slide toward the 90 degree, or vertical position. The section (believe it or not) has been successfully transferred to the surface of the slide!

After the distal end of the slide has been momentarily pressed against a paper towel to drain off excess of glucose, the slide is grasped in the left hand and held in the horizontal plane. With the right hand, a cover slip is swept along the

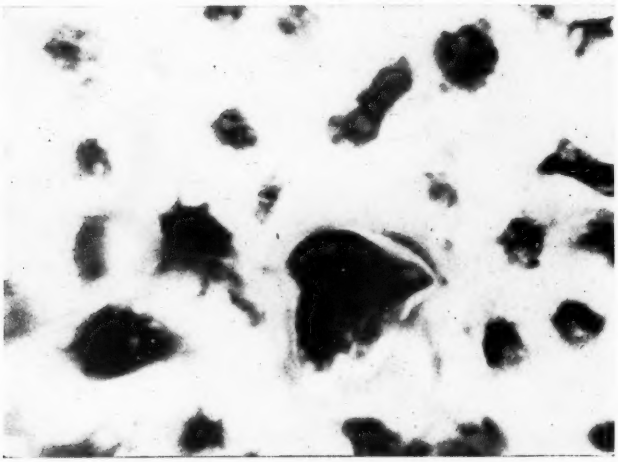

Fig. 8. Malignant osteoblasts, including 1 giant form, with 2 large nucleoli, from a case of osteogenic sarcoma. Note the ground-glass appearance of the osteoid matrix. Compare Figure 4. Polychrome methylene blue, ×970.

upper surface of the slide until it reaches the edge of the tissue. Holding this cover slip at an angle of 45 degrees to the surface of the slide gathers up enough glucose solution to rid the preparation of air bubbles when the cover slip is merely allowed to fall by its own weight. The rest of the operation very simply consists of wiping dry the edges and under surfaces of the mount, which is now ready for examination.

Extremely small bits of tissue such as those provided by needle aspirations and "coring" methods must be elevated above the freezing stage prior to cutting. With them as with larger blocks, the principle of minimal freezing should be applied for best results. The special technique involved is as follows: Place a fair-sized drop of saline solution on the surface of the stage and freeze it into a mound of ice. Next, moisten the midget specimen to be sectioned and place it on the upper surface of the mound. A minimal amount of additional freezing imparts the requisite rigidity to the tissue chiefly through solidification of the surrounding film of saline solution. With the microtome knife previously adjusted to the correct level, the steps necessary for removing tissue flakes are exactly similar to those detailed in the foregoing.

The successful sectioning of lymph nodes is deserving of special comment, since many technicians find the handling of these structures exasperating, to say the least. The principle to remember is that the presence of the nodal capsule, however thin, assists greatly in maintaining intact the sections which are cut. By the same token, when a bisected or otherwise partitioned node is to be processed, the capsular surface, even if rounded, should be offered to the cutting edge of the microtome knife. Great care must be exercised *not* to freeze the tissue excessively, and preliminary moistening should be minimal. Like brain tissue, gastric mucosa, and endometrium, the substance of the average lymph node contains a considerable amount of "tissue juice" so that the addition of saline solution for purposes of sectioning is often unnecessary.

As a real timesaver in selecting properly formalinized blocks of tissue which are to be processed later as permanently stained mounts, the rapid freezing technique serves an added and very useful purpose. Cutting and mounting are readily accomplished in the manner previously described. The staining, however, should consist of only a momentary "dip" in a solution of polychrome methylene blue which has been slightly acidified. Failure to observe these deviations from the "routine recipe" results in mounts which are almost impervious to light and which exhibit a very narrow range of color differentiation.

Exposure to light and air induces a rapid fading of polychrome methylene blue sections. If preservation of selected mounts is desired, sealing the edges of the cover slips with a cement substance and storing of the slides in the labor-

Fig. 9. Grade 2 adenocarcinoma of the colon. Polychrome methylene blue, ×100.

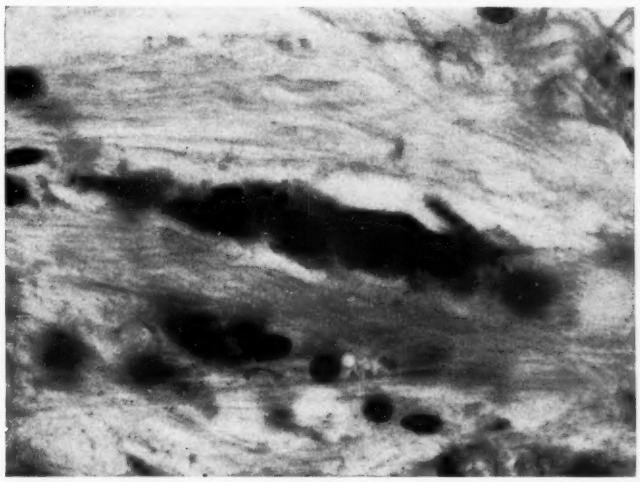

Fig. 10. The single filing of cytologically malignant cells (macronucleoli, and so forth) stands out in sharp contrast to the pale-staining collagen. Polychrome methylene blue, ×1,000.

atory icebox make the preparations semipermanent. By this means, mounted sections of coccidiomycotic granulomas and other exotic conditions may be made to preserve their "freshness" for periods in excess of 5 years.

The following may be listed as some of the commoner "misbehaviors" of tissue flakes along with their causes and the means of correcting them.

1. The section fails to separate completely from the underlying frozen portion of the block. This common fault is produced by the presence of irregular tongues or tags of tissue on the proximal edge of the block. It can be avoided by

careful preliminary preparation of the block, but when it occurs the remedy consists of employing the scalpel to remove the frozen projecting tag. Haste is here essential, since the operation is being carried out while the still unsectioned portion of the block is commencing to thaw.

2. Inability to transfer the section from the microtome blade to the forefinger: Such a difficulty is often owing to the presence of too much saline solution, particularly on the under surface of the blade. This fault begets another nuisance, namely, that of saline solution moistening the upper surface of the frozen block on the reverse sweep of the knife. Periodic wiping of the knife surfaces is the answer to this problem.

3. Curling of the section on the surface of the knife: When this phenomenon is observed with any section except the first, one usually finds that no angle exists between the edge of the block and the knife. Other reasons lie either in the section being too thick (knife dullness) or the tissue being insufficiently frozen. The remedy in all 3 instances is obvious.

4. The occurrence of wavy sections containing knife lines: These defects can usually be avoided by making sure that the 4 adjustments on the hinged mechanism which operates the knife are set so as not to allow for any up-and-down play of the latter. Occasionally the source of the trouble is to be found in an unstable freezing stage which has been weakened by regrooving.

5. Sections may adhere to the glass lifter. The presence on the lifter of mucus or grease is the commonest cause of this annoyance. Prevention lies in keeping the business end of the lifter scrupulously clean at all times.

6. "Disintegration" of the section when placed in the saline solution: The overenergetic freezing of tissues sometimes causes this tissue-commotion. The chief offender, however, is static electricity on the surface of the saline solution, and the frequency of its occurrence varies considerably with different conditions of humidity and so forth. This vexation can for the most part be avoided by agitating the saline solution with the glass lifter preparatory to making the first section.

Figure 1 illustrates the essentials of the working tools. Figures 2 through 10 depict photographically results of preparing certain so-called difficult tissues by the fresh freezing method.

CONCLUSIONS

1. The employment of fresh frozen section techniques under ideal conditions can be of great advantage to the patient who is undergoing a surgical operation.

2. Difficulties with the development of rapid sectioning technique for fresh tissues are not insurmountable.

3. A method whereby such tissues may be rapidly sectioned and stained is described in some detail.

4. Cognizance is taken of certain faults commonly encountered with the method, and the means for correcting these are outlined.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

HIS personal concepts of cardiac therapy are presented by Dr. Stewart[1] in an interesting and comprehensible style. Beginning with a discussion of congestive failure, he proceeds with a detailed consideration of the mercurial diuretics, digitalis preparation, and anticoagulant drugs. After a chapter on the cardiac irregularities, the succeeding 14 chapters are devoted to the various etiologic types of heart disease and those conditions which may simulate cardiac disease. The latter portion of the book covers diseases of the pericardium, mediastinum, endocardium, and various therapeutic problems such as cardiac trauma, surgical management of the cardiac patient, and the effects of various electrolytes on the heart. Chapters on what to tell the patient with heart disease, prevention of heart disease, and diet management conclude the volume.

The book in areas is admittedly repetitious in order to improve its value as a reference text. There is considerable material not restricted to treatment which gives the reader a basis for the therapeutic ideas outlined. The preface warns that the material is in a sense dogmatic and reflects the author's personal notions. Opposing views are presented, for the most part, in adequate detail. Stewart lists triple bromides as a sedative to be used in the treatment of congestive failure but does not warn that this preparation contains substantial amounts of sodium and potassium which may be hazardous to the cardiac patient. The statement that "large amounts of fluids may be given intravenously" in the treatment of anuria resulting from mercurial therapy will be challenged. A chapter on quinidine might well be included in a book on cardiac therapy. Those without previous experience with this drug will certainly be cautious in its use in combination with digitalis after reading this volume. This is a controversial subject, but most evidence indicates that this apparently dangerous combination is manifest only when an excessive or toxic amount of digitalis is present. Although this is implied a more complete discussion would seem to be indicated. The author says that quinidine speeds up the conduction of the excitation wave of auricular fibrillation and therefore tends to perpetuate the circus movement (if such exists—reviewer's note). This is incorrect according to other writers on the subject. Quinidine slows the conduction time of the wave and thus tends to perpetuate the circus movement.

The student and general practitioner will appreciate this volume. The young cardiologist will gain much from Dr. Stewart's conservative opinions and wise counsel regarding the over-all management of the cardiac patient.

JOHN A. MART.

THE short monograph of 45 pages *Roentgenuroskopie; Nierenbecken und -kelche, Harnleiter, Blase, Harnröhre*[2] deals with the fluoroscopic observation of the urinary tract. The film is then exposed at the opportune moment. The author has used the method in over 1,000 cases and he is convinced that it has definite advantages over so called blind urography. Artefacts which might easily lead to the false diagnosis of stricture, tumor, or ureteropelvic obstruction by aberrant vessels are readily identified. Radiotranslucent calculi, which would escape detection by routine pyelography, are often found by this method.

The technique is not new, for it was first described over 25 years ago by Papin and others. It has, however, not found the application which it deserves because it is too cumbersome and time-consuming for ordinary clinical practice.

This excellent monograph, which has the merit of brevity, is well written. The illustrations are very good.

FREDERICK A. LLOYD.

THE book *Electrocardiography in Practice*[3] has been rewritten to include recent advances in the field of electrocardiography, some of which are practical and some theoretical. The outstanding feature of the work is its practicality. The material is very well organized and presented as dogmatically as is possible under the circumstances. The tracings are well reproduced and usually include augmented unipolar limb leads and 3 to 6 CF or V precordial leads.

A feature which is particularly instructive is the inclusion of excellent summaries of the history, physical examination, and laboratory findings pertinent to each tracing. The section on the history of electrocardiography especially is interesting. The book can be wholeheartedly recommended to practitioners of medicine.

HUGH A. FLACK.

[1]CARDIAC THERAPY. By Harold J. Stewart, M.D. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., 1952.

[2]ROENTGENUROSKOPIE; NIERENBECKEN UND -KELCHE, HARNLEITER, BLASE, HARNRÖHRE. By Dr. Med. Habil. G. W. Günther. Stuttgart: Georg Thieme, 1952.

[3]ELECTROCARDIOGRAPHY IN PRACTICE. By Ashton Graybiel, M.D., Paul D. White, M.D., Louise Wheeler, A.M., and Conger Williams, M.D. 3rd ed. Philadelphia, London: W. B. Saunders Co., 1952.

THE textbook of 855 pages entitled *Textbook of Surgery*[1] is a collection of contributions from various members of the staff of McGill University and the Royal Victoria Hospital, Montreal, Canada. It is illustrated by 46 color plates by Dr. Frank H. Netter. The color plates, though somewhat diagrammatic, are highly descriptive and good teaching material for students. There are also 460 text illustrations composed of line and halftone drawings by Miss Helen MacArthur which are very well done; there are likewise some black and white and color photographs. An adequate index is included.

The material in the text is divided into 42 chapters embracing the usual subjects included in a textbook of surgery. The method of presentation of the topics is very good, the text is readable, in excellent English and as up to date as any textbook can be. The quality of the paper and the print is excellent.

The surgical faculty of McGill University is to be congratulated for the production of this fine surgical textbook.

THOMAS C. DOUGLASS.

THE 438 page monograph on surgery of the biliary tract *Chirurgie des voies biliaires de l'adulte et du nourrisson*[2] comes from the Hospital of Saint Antone in Paris. The subject of biliary tract surgery is rather thoroughly covered. The table of contents shows the division of the text into sections on anatomy, physiology, lesions of the biliary tract, various means at the disposal of the surgeon, techniques, preparation of the patient, the anesthesia, advantages and disadvantages of various types of operative procedures, and finally direct application of these various points. The last chapter, the tenth, is concerned with surgical jaundice of the newborn. No index is included.

The text is well illustrated, by both line drawings and very good reproductions of cholangiograms to illustrate various points. The authors have obviously perfected the technique of cholangiography and used it widely. Photographs of the reproductions of x-ray films are excellent. Small insets with line drawings clarify the interpretation of the roentgenograms and add a great deal to the illustrative value of the cholangiograms.

The general organization of the text is somewhat different from the usual English textbook. Credit is given to some of the leaders in the field of biliary tract surgery in the introduction and some reference is made to authors of various procedures, but in general the procedures are described without particular reference to the origin or development of this particular type of operative procedure. Although the monograph is not a reference work, it is thorough and exhaustive in its study of the various procedures which are currently being used in the surgery of the biliary tract. The conclusions which the authors reach are, in general, similar to those popular in America today, but with some slight differences. One of these is the emphasis which is placed on cholangiography, which obviously has been developed more fully by these authors than is true in many clinics in the United States.

The reviewer has enjoyed reading this monograph and believes that it is an addition to the library of any surgeon who has a particular interest in the field of biliary tract surgery.

THOMAS C. DOUGLASS.

IN the preface of *Handbook of Orthopaedic Surgery*[3] the author states that "the purpose of this book is to present for the consideration of the medical student and the general practitioner the fundamental facts and principles of orthopaedic surgery as concisely as possible and yet in a sufficient detail to convey a well-rounded knowledge of the subject."

The author has succeeded admirably in accomplishing his purpose. The emphasis is on the evaluation and treatment of the patient as a whole rather than on regional problems. Each sentence has a pertinent thought for the reader. The opinions expressed represent judgment that has come from years of experience and are on the conservative side. Reference to this work in specific orthopedic problems will give the general practitioner a helpful guide in his own work and an idea of what care his patient may expect in the hands of the orthopedic surgeon.

Reproductions of roentgenograms replace the line sketches of roentgenograms used in previous editions. The reviewer believes, however, that the clarity of previous editions resulted in part from the extensive line drawings representing composite x-ray examinations.

A few minor criticisms might be mentioned. It seems to the reviewer that insufficient emphasis is placed on the diagnosis and treatment of congenital dysplasia of the hip. Those using this book for reference need every available help in diagnosing and initiating early treatment for this condition. On page 156, Figure 63 represents a method of hip arthroplasty which is of historic interest only, but one might conclude from the text that it is currently popular. Healing phases of fresh fractures could be illustrated by diagrams to supplement the text. On page 343 emphasis is placed on a healing time of 3 months for bone graft, and the suggestion is made that the plaster then be bivalved and physical therapy started. Perhaps evaluation by clinical and roentgenologic examination to determine the state of healing should be emphasized in these highly individualized cases. The helpful effect of roentgen-ray therapy of bursitis of various regions of the body is not discussed. More frequent explanations of the modalities of physical therapy would guide the

[1] TEXTBOOK OF SURGERY. Edited by H. F. Moseley, M.A., D.M., M.Ch.(Oxon.), F.A.C.S.(Eng.), F.R.C.S.(C). With a foreword by G. Gavin Miller, M.D., C.M., M.Sc., F.R.C.S.(C), F.A.C.S. St. Louis: The C. V. Mosby Co., 1952.

[2] CHIRURGIE DES VOIES BILIAIRES DE L'ADULTE ET DU NOURRISSON; TECHNIQUE ET TACTIQUE. By M. Champeau and P. Pineau. With collaboration by A. Prochiantz and Mme S. Desvignes. Paris: Masson et Cie, 1952.

[3] HANDBOOK OF ORTHOPAEDIC SURGERY. By Alfred Rives Shands, Jr., B.A., M.D. In collaboration with Richard Beverly Raney, B.A., M.D. 4th ed. St. Louis: The C. V. Mosby Co., 1952.

reader rather than the single statement that "physical therapy is instituted." The majority of practitioners do not have others to call upon for physical therapy but must guide the patient with simple measures in the office or at home.

An earlier edition was an inspiration to the reviewer as a senior medical student. To review the new edition is like sitting down for a visit with an old friend who has gained poise and grace with the passage of time.

KENATH H. SPONSEL.

IN THE 138 page treatise *Commotio Cerebri*[1] by Cyril B. Courville, the author traces the development of our present day concept of concussion, contusion, and compression, through legend, history, and present day writings. The author writes at some length to show that concussion is not necessarily accompanied by loss of consciousness. He divides concussion into 7 forms varying from the mildest, which consists of transitory motor weakness, dizziness or blurring of vision without impairment of consciousness, to the most severe degree, which destroys the patient outright "without any evidence of significant damage to the brain."

There are chapters on the mechanism of concussion, the development of edema, and of the cellular pathology associated with these. The author repeatedly impresses the reader with his feeling that the postconcussion syndrome is a true clinical entity and not simply a psychic state or malingering. He also believes that it is important to establish the diagnosis of concussion early, to anticipate and prevent postconcussion neurosis, and emphasizes that a sympathetic approach tends to shorten the period of convalescence. Postconcussion headaches, which he states are secondary to a vasomotor instability resulting from the injury, respond to the intramuscular injection twice weekly of prostigmine methyl sulfate in a dilution of 1:2,000 plus 15 milligrams of prostigmine bromide given orally 3 times a day.

"It can no longer be reasonably assumed that the characteristic residual symptoms of Commotio Cerebri are all to be lightly dismissed as a postconcussion neurosis or malingering. While purely psychic postconcussion manifestations may also occur, the counterfeit need not be confused with the genuine. An intelligent, comprehensive and up-to-date therapeutic approach to the problem has potentialities both for more prompt relief of the patient's symptoms and lowering of costs to insurance carriers."

JOSEPH TARKINGTON.

THE monograph on bone grafts *Die Konservierung von Knochengewebe für Transplantionen*[2] is written by the chief surgeon of the University of Basel. The author gives evidence of a wide clinical experience. He reports the results of a large series of experiments on bone grafts which he has carried out at his clinic, reviews the literature, and includes a short summary of all the important articles pertaining to the subject.

One section concerns bone grafts in general, the other deals with the preservation of bone tissue (bone bank). The text is supplemented by 147 excellent and convincing illustrations.

Dr. Roth deals with the theoretical as well as the practical problems of a bone bank. He agrees that there is no recognized standard method of preserving bone. The purpose of the monograph is to give a cross section of the present knowledge of bone transplants and to stimulate interest in others to work on the many problems that still exist.

He points out that it is generally accepted that bone grafts are replaced by new bone tissue. There is a difference of opinion as to whether individual cells remain as a vital and active part of the graft, or whether the entire graft is replaced by a transplant formed from the bed of the host.

The disadvantages of autogenous grafts are: (1) the difficulty of obtaining large grafts, (2) obtaining adequate grafts in children, and (3) the difficulty of dealing with multiple bone lesions. Furthermore, taking an autogenous graft frequently prolongs the period of convalescence, and this factor increases the need for a bone bank.

The danger of infection formerly acted as the chief deterrent to the use of homogenous bone grafts. Availability of antibiotics has greatly reduced this danger. The retention of the vitality of the cells in a transplant is not of primary importance. The biologic function of a graft is to stimulate osteogenesis and form new bone in the host.

Boiled or macerated bone when used as a graft is shown to be ineffective because the osteogenetic qualities have been destroyed by boiling or macerating. Conservation by freezing is possible although extreme cold is injurious. The optimum temperature is established by the author as between 12 degrees and 20 degrees centigrade. He stresses the advantage of the use of a coating of liquid paraffin in preserving bone tissue. Other authorities use an aqueous solution of merthiolate as a preservative. Some injury to the bone tissue is associated with either method. More time is required to obtain a solid union with a homogenous graft than with an autogenous graft. The author has found the results of grafts from a bone bank surprisingly good. He points out, however, that complications may arise and that bone bank technique has not been standardized.

He emphasizes the need for exact surgical technique at the time the bone material is obtained. In addition to insisting upon sterile technique, he checks the grafts for infection at the time they are removed and again when the graft is used. He does not use bone grafts that have been preserved for more than 4 weeks.

The author cites graphically a number of cases in which he used bone grafts successfully for ununited fractures, bone cysts, and reconstruction surgery.

[1] COMMOTIO CEREBRI; CEREBRAL CONCUSSION AND THE POSTCONCUSSION SYNDROME IN THEIR MEDICAL AND LEGAL ASPECTS. By Cyril B. Courville, M.D. Los Angeles: San Lucas Press, 1953.

[2] DIE KONSERVIERUNG VON KNOCHENGEWEBE FÜR TRANSPLANTATIONEN. By Hans Roth. Wien: Springer-Verlag, 1952.

In Dr. Roth's opinion homogenous grafts will not completely replace the use of autogenous grafts. The type of method will be determined by selection of individual cases. EMIL D. W. HAUSER.

THE new book by A. R. Hollender and co-authors on *The Pharynx; Basic Aspects and Clinical Problems*[1] is well done, well illustrated, and covers the field satisfactorily so far as 550 pages will permit.

The various portions of the pharynx and related fields are covered in an adequate manner. Surgical technique has not been stressed. The indications for therapeutic measures and the treatments listed for the various lesions of the pharynx and related regions are conservative and may be followed on the whole with relative safety. The chapter on roentenographic examinations of the pharynx is well presented and illustrated and fills a need for a book of this type. The chapter on the palate and uvula, especially those portions regarding the comparative anatomy and physiology, is well worth reading as this region of the pharynx has not received a great deal of attention in the recent literature. An informative bibliography is listed at the end of each chapter.

Dr. Hollender and his co-authors are to be congratulated upon an excellent presentation of the basic aspects and clinical problems of the pharynx.

HOWARD C. BALLENGER.

[1]THE PHARYNX; BASIC ASPECTS AND CLINICAL PROBLEMS. Edited by Abraham R. Hollender, M.D., F.A.C.S. Chicago: The Year Book Publishers, Inc., 1953.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in ths interests of our readers and as space permits.

LA FECONDAZIONE ARTIFICIALE UMANA. By Giuseppe Abruzzese. 400 pages, illustrated. Lire 1300. Firenze: La Voce Scientifica, 1953.

GASTRECTOMIA PARCIAL; RESULTADOS NA ÚLCERA GÁSTRICA E DUODENAL. By Lúcio Galvão. 163 pages, with 34 illustrations. Rio de Janeiro, 1952.

X-RAY SIEVE THERAPY IN CANCER; A CONNECTIVE TISSUE PROBLEM. By Benjamin Jolles, M.D., D.M.R. With a foreword by Sidney Russ. 192 pages, with 51 illustrations. $6.00. Boston: Little, Brown & Co., 1953.

FUNCTIONAL AND SURGICAL ANATOMY OF THE HAND. By Emanuel B. Kaplan, M.D., F.A.C.S. 288 pages, with 132 illustrations. $10.00. Philadelphia, London, Montreal: J. B. Lippincott Co., 1953.

ZEITLOSES UND ZEITGEBUNDENES IN DER CHIRURGIE. By Prof. Dr. Rudolf Nissen. 32 pages. DM 2. Stuttgart: Georg Thieme, 1953.

PHYSICAL EXAMINATION OF THE SURGICAL PATIENT. By J. Englebert Dunphy, M.D., F.A.C.S., and Thomas W. Botsford, M.D., F.A.C.S. 326 pages, with 188 illustrations. $7.50. Philadelphia, London: W. B. Saunders Co., 1953.

HEART AND CIRCULATION; DIAGNOSIS AND TREATMENT. By Meyer Sclar, M.D., F.A.C.C. Assisted by Jacob Melnick, M.D. 358 pages, illustrated. $7.50. New York: Froben Press, Inc., 1953.

A MODERN PRACTICE OF OBSTETRICS. By D. M. Stern, M.A., M.B., B.Ch.(Cantab.), F.R.C.S., F.R.C.O.G., and C. W. F. Burnett, M.D.(Lond.), F.R.C.S., F.R.C.O.G. Line drawings by Susan M. Robinson. 248 pages, with 140 illustrations. $7.00. London: Baillière, Tindall and Cox; Baltimore: The Williams Wilkins Co., 1952

MORRIS' HUMAN ANATOMY: A COMPLETE SYSTEMATIC TREATISE. Edited by J. Parsons Schaeffer, A.M., M.D., Ph.D., Sc.D., D.Litt. 11th ed. 1,718 pages, with 1,220 illustrations. $16.00. New York, Toronto: The Blakiston Co., 1953.

THE ROENTGEN ASPECTS OF THE PAPILLA AND AMPULLA OF VATER. By Maxwell H. Poppel, M.D., F.A.C.R., Harold G. Jacobson, M.D., F.A.C.R., and Robert W. Smith, M.D. 195 pages, with 106 illustrations. $8.50. Springfield, Ill.: Charles C Thomas, 1953.

SACRAL NERVE-ROOT CYSTS; ANOTHER CAUSE OF THE SCIATIC OR CAUDA EQUINA SYNDROME. By I. M. Tarlov, M.D. 134 pages, with 65 illustrations. $6.50. Springfield, Ill.: Charles C Thomas, 1953.

TRANSACTIONS OF THE AMERICAN GOITER ASSOCIATION, 1952 ANNUAL SESSION, MAY 1, 2, AND 3, CHASE HOTEL, ST. LOUIS, MISSOURI. 429 pages, illustrated. $12.50. Springfield, Ill.: Charles C Thomas, 1953.

ATLAS OF TUMOR PATHOLOGY. Published by the Armed Forces Institute of Pathology under the Auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council. Section IV, Fascicle 14: Tumors of the Thyroid Gland. By Shields Warren, M.D., and William A. Meissner, M.D. 97 pages, with 82 illustrations. $1.75. Section IV, Fascicle 15: Tumors of the Parathyroid Glands. By Benjamin Castlemen, M.D. 74 pages, with 53 illustrations. $.65. Section V, Fascicle 17: TUMORS OF THE LOWER RESPIRATORY TRACT. By Averill A. Liebow, M.D. 189 pages, with 249 illustrations. $1.25. Section VIII, Fascicles 31b and 32: Tumors of the Male Sex Organs. By Frank J. Dixon, M.D., and Robert A. Moore, M.D. 179 pages, with 135 illustrations. $1.50. Section X, Fascicles 35 and 37: Tumors of the Central Nervous System. By James W. Kernohan, M.D., and George P. Sayre, M.D. 129 pages, with 126 illustrations. $.90. Washington: Armed Forces Institute of Pathology, 1952 and 1953.

LO ESENCIAL EN ORTOPEDIA. By Philip Wiles, M.S. (Lond.), F.R.C.S. (Eng.), F.A.C.S. Translated by Dr. Leoncio Luis Fernandez, Dr. Alberto O. Calzaretto, and Dr. Mario W. Acrich Arrues. 496 pages, with 365 illustrations. Buenos Aires: Editorial Artecnica, 1953.

EPIDEMICS IN COLONIAL AMERICA. By John Duffy. 274 pages. $4.50. Baton Rouge: Louisiana State University Press, 1953.

A COLLECTION OF UROGENITAL DRAWINGS; ANATOMY, ANOMALIES, GROSS PATHOLOGY, 1915–1952. By William P. Didusch. 222 pages, with 243 figures. New York: American Cystoscope Makers, Inc., 1952.

DIE LUNGENRESEKTIONEN. By Prof. Dr. A. Lezius. With a preface by Prof. Dr. R. Nissen. 143 pages, with 149 illustrations. DM 49.80. Stuttgart: Georg Thieme, 1953.

CLINICAL CONGRESS OF AMERICAN COLLEGE OF SURGEONS

HAROLD L. FOSS, Danville, Pennsylvania, *President*
FRED W. RANKIN, Lexington, Kentucky, *President-Elect*

PRELIMINARY PLANS FOR 39TH CLINICAL CONGRESS, THE CONRAD HILTON, CHICAGO, OCTOBER 5 TO 9, 1953

THE GENERAL scientific sessions of the Congress will begin this year with a panel discussion at 10:30 a.m. on Monday, October 5. It should be noted that this opening scientific session takes the place of the General Assembly which opened previous Congresses. This year also two clinicopathology conferences will be included in the afternoon programs of the Congress, and there will be three symposia.

Only three general evening sessions are planned, for Monday, Wednesday, and Friday evenings. The evenings of Tuesday and Thursday are being left free for committee meetings, the motion picture symposium, and other special group activities.

In addition to the panel discussion sessions to be held each afternoon, six surgical specialties will hold panel discussion programs on Friday afternoon. Also, 3 day programs for gynecology and obstetrics, ophthalmology, and otolaryngology are being arranged by the Advisory Councils for these three specialties. The Surgical Forum Committee is planning 12 Forum sessions. Six postgraduate courses will be given on the forenoons of Tuesday, Wednesday, Thursday, and Friday.

Because seating space for the postgraduate courses will be limited, and it is important to make reservations as soon as possible, this issue of SURGERY, GYNECOLOGY AND OBSTETRICS carries the outline of the postgraduate courses in some detail. The August issue will carry other details of the Congress program, and the September issue will carry the entire program. Registration fee is $5.00 per postgraduate course. Sessions will run from 8:30 a.m. to 11:30 a.m. Registration forms are available from the American College of Surgeons, 40 East Erie Street, Chicago 11, Illinois.

POSTGRADUATE COURSES

PREOPERATIVE AND POSTOPERATIVE CARE

WALTER G. MADDOCK, M.D., F.A.C.S., Chairman.

Tuesday, October 6

The Effect of Operation on Kidney Function. CARL A. MOYER, M.D., F.A.C.S., St. Louis.

Common Mistakes in the Administration of Water and Electrolyte. ROBERT ELMAN, M.D., F.A.C.S., St. Louis.

When Is Oxygen Beneficial? PHILIP B. PRICE, M.D., F.A.C.S., Salt Lake City.

Thromboembolism; a Continuing Problem. MICHAEL E. DEBAKEY, M.D., F.A.C.S., Houston.

Wednesday, October 7

Clinical Lessons from Blood Volume Studies. CHAMP LYONS, M.D., F.A.C.S., Birmingham.

Blood, Plasma, Plasma Fractionization Products; Their Uses and Abuses. J. GARROTT ALLEN, M.D., F.A.C.S., Chicago.

Postoperative Pulmonary Complications; Their Avoidance and Treatment. ROBERT M. JANES, M.D., F.A.C.S., Toronto.

Cardiac Arrest and Resuscitation. EGBERT H. FELL, M.D., F.A.C.S., Chicago.

Thursday, October 8

Meeting the Supranormal Dietary Requirements of Surgical Patients. JONATHAN E. RHOADS, M.D., F.A.C.S., Philadelphia.

The Effect of Nutritional Management in Recovery from Burns. EVERETT IDRIS EVANS, M.D., F.A.C.S., Richmond.

Problems Peculiar to Surgery of Infants and Children. CLIFFORD D. BENSON, M.D., F.A.C.S., Detroit.

Surgery in the Elderly. CHARLES C. LUND, M.D., F.A.C.S., Boston.

Friday, October 9

Traumatic Endocrinology and Hormone Administration. FRANCIS D. MOORE, M.D., F.A.C.S., Boston.

How Gastrointestinal Distention Develops, and Its Prevention. WALTER G. MADDOCK, M.D., F.A.C.S., Chicago.

Observations on the Reduction of Intestinal Distention with Long Tubes. RUDOLPH J. NOER, M.D., F.A.C.S., Louisville.
The Best Results from Antibiotic Therapy. WILLIAM A. ALTEMEIER, M.D., F.A.C.S., Cincinnati.

SURGERY OF THE SMALL AND THE LARGE BOWEL

R. KENNEDY GILCHRIST, M.D., F.A.C.S., Chairman.

The following will participate in the presentation of this Postgraduate Course:

WILLIAM A. ALTEMEIER, M.D., F.A.C.S., Cincinnati.
EUGENE M. BRICKER, M.D., F.A.C.S., St. Louis.
RALPH COLP, M.D., F.A.C.S., New York.
CLARENCE DENNIS, M.D., F.A.C.S., Brooklyn.
CLAUDE F. DIXON, M.D., F.A.C.S., Rochester, Minnesota.
ROBERT E. GROSS, M.D., F.A.C.S., Boston.
GEORGE HAAS, M.D., Chicago.
CHARLES G. JOHNSTON, M.D., F.A.C.S., Detroit.
EDWIN M. MILLER, M.D., F.A.C.S., Chicago.
WALTER L. PALMER, M.D., Chicago.
WILLIS J. POTTS, M.D., F.A.C.S., Chicago.
FRED O. PRIEST, M.D., Chicago.
ROBERT A. SCARBOROUGH, M.D., F.A.C.S., San Francisco.
DAVID STATE, M.D., F.A.C.S., Minneapolis.
RUPERT B. TURNBULL, M.D., F.A.C.S., Cleveland.
OWEN H. WANGENSTEEN, M.D., F.A.C.S., Minneapolis.
CLAUDE E. WELCH, M.D., F.A.C.S., Boston.

Tuesday, October 6

Physiology of Large and Small Bowel
Congenital Anomalies
  Small Bowel
  Large Bowel
  Hirschsprung's Disease
  Rectum
Intestinal Obstruction
  Diagnosis
  Physiology
  Fluids and Electrolytes
  Tubes and Their Use
  Intussusception
  Surgical Treatment

Wednesday, October 7

Inflammatory Diseases of Small Bowel
  Regional Enteritis
Ulcerative Colitis
  Medical Management and Diagnosis
  Surgical Treatment
  Indications for:
    Total Colectomy and Ileostomy
    Hemorrhage and Its Control
    Carcinoma
    Status of Vagotomy
    Ileostomy and Its Care and Types of Bags
Tuberculosis of Colon, Ileocolitis, Actinomycosis
Amoebic Colitis

Thursday, October 8

Diverticulitis of Colon
Carcinoma
  Preoperative Treatment and Treatment of Obstructed Lesions
  Pathology
  Carcinoma of Colon to Midsigmoid
  Low-Lying Lesions
  Surgical Treatment of Adherent Lesions
  Second Look Operation
  Palliative Resection and Care of Those with Inoperable Lesions and Those with Recurrences
  Anesthesia in the Aged and Poor Risk Patients and Surgery in Aged and Poor Risk Patients

Friday, October 9

Rectal Surgery
  Treatment of Congenital Anomalies
  Diagnosis of Rectal Pathology
  Hemorrhoids—Surgical and Injection Treatment
  Fissures, Crypts, Ulcers
  Fistulas—Tuberculous and Nonspecific
  Prolapse
    2nd degree
    3rd degree
  Pruritus Ani
  Condyloma Accuminata and Venereal Warts
  Traumatic Injuries
  Anesthesia
  Carcinoids, Lymphomas

CARDIOVASCULAR SURGERY

EGBERT H. FELL, M.D., F.A.C.S., Chairman.

Tuesday, October 6

Surgical Problems Concerning the Peripheral Arterial System.
Moderator: GEZA DE TAKATS, M.D., F.A.C.S., Chicago.
Care of the Arteriosclerotic Limb. NELSON W. BARKER, M.D., Rochester, Minnesota.
Treatment of Complications of the Arteriosclerotic Limb. LELAND S. MCKITTRICK, M.D., F.A.C.S., Brookline, Massachusetts.
Acute Peripheral Arterial Occlusion. NORMAN E. FREEMAN, M.D., F.A.C.S., San Francisco.
Surgical Problems Concerning the Peripheral Venous System.
Moderator: J. ROSS VEAL, M.D., F.A.C.S., Washington.
The Treatment of Thrombophlebitis and Its Complications. WILLIAM D. HOLDEN, M.D., F.A.C.S., Cleveland.
The Treatment of Varicose Veins. THOMAS T. MYERS, M.D., Rochester, Minnesota.
The Use of Anticoagulants in Vein Pathology. JOHN H. OLWIN, M.D., F.A.C.S., Chicago.

Wednesday, October 7

Aneurysms and Arteriovenous Fistulas.
Moderator: HARRIS B. SHUMACKER, JR., M.D., F.A.C.S., Indianapolis.
Participants: FRANK L. GERBODE, M.D., F.A.C.S., San Francisco; WILLIAM S. DYE, M.D., Chicago; EDWARD J. JAHNKE, JR., Major (M.C.) U.S.A., Washington.
Cardiac Trauma.
Moderator: DANIEL C. ELKIN, M.D., F.A.C.S., Atlanta.
Trauma Due to Cardiac Hypoxia. JULIAN JOHNSON, M.D., F.A.C.S., Philadelphia; WILLIAM O. MCQUISTON, M.D., Peoria, Illinois.
Diagnosis and Treatment of Acute Tamponade. MARK M. RAVITCH, M.D., F.A.C.S., New York.
The Care of Stab and Gunshot Wounds of the Heart. DUANE CARR, M.D., F.A.C.S., Memphis.

Thursday, October 8

Surgery for Congenital Anomalies of the Heart and Great Vessels.
Moderator: ALFRED BLALOCK, M.D., F.A.C.S., Baltimore.
When Should the Patient with Congenital Heart Disease Be Referred to the Surgeon? BENJAMIN M. GASUL, M.D., Chicago.
Surgery for the Congenital Heart of the Cyanotic Group. RICHARD L. VARCO, M.D., F.A.C.S., Minneapolis.

Problems Concerning Patent Ductus Arteriosus, Coarctation of the Aorta, and the Double Aortic Arch. JOHN C. JONES, M.D., F.A.C.S., Los Angeles.

Surgical Problems Arising from Acquired Heart Disease.

Moderator: EGBERT H. FELL, M.D., F.A.C.S., Chicago.

When Should the Patient with Acquired Heart Disease be Referred to the Surgeon? OGLESBY PAUL, M.D., Chicago.

Mitral Stenosis. DWIGHT E. HARKEN, M.D., F.A.C.S., Boston.

Surgery for Aortic Stenosis and Mitral and Aortic Insufficiency. THOMAS J. E. O'NEILL, M.D., Philadelphia.

Friday, October 9

The Latest Developments in the Field of Cardiovascular Surgery.

Surgery of the Peripheral Venous System. ROBERT R. LINTON, M.D., F.A.C.S., Brookline, Massachusetts.

Vessel Grafts. CHARLES A. HUFNAGEL, M.D., F.A.C.S., Washington.

Arterial Bank. JERE W. LORD, JR., M.D., F.A.C.S., New York.

Surgery of the Peripheral Arterial System. ORMAND C. JULIAN, M.D., F.A.C.S., Chicago.

Congenital Lesions of the Heart and Great Vessels. ROBERT E. GROSS, M.D., F.A.C.S., Boston.

Surgery for Acquired Heart Disease. ROBERT P. GLOVER, M.D., Philadelphia.

Hypothermia. WILFRED G. BIGELOW, M.D., Toronto.

Portacaval Shunt in Portal Hypertension. ARTHUR H. BLAKEMORE, M.D., New York.

Heart-Lung Apparatus. JOHN H. GIBBON, JR., M.D., F.A.C.S., Philadelphia.

OBSTETRICS AND GYNECOLOGY

HERBERT E. SCHMITZ, M.D., F.A.C.S., Chairman.

Tuesday, October 6

Prolapse of the Uterus—Relaxed Vaginal Outlet.

Moderator: JOSEPH L. BAER, M.D., F.A.C.S., Chicago.

Applied Anatomy in Relation to Management. JOHN W. HUFFMAN, M.D., F.A.C.S., Chicago.

Manchester-Fothergill Operation. RALPH A. REIS, M.D., F.A.C.S., Chicago.

Vaginal Hysterectomy for Uterine Prolapse. EDWARD D. ALLEN, M.D., F.A.C.S., Chicago.

Discussion: RICHARD W. TELINDE, M.D., Baltimore.

Treatment of Enterocele Complicating Prolapse. RALPH E. CAMPBELL, M.D., F.A.C.S., Madison.

Treatment of Vaginal Prolapse. LOUIS E. PHANEUF, M.D., F.A.C.S., Boston.

Discussion: EDWARD A. EDWARDS, M.D., F.A.C.S., Boston.

Wednesday, October 7

Abortion

Moderator: NICHOLSON J. EASTMAN, M.D., Baltimore.

Definition of and Classification of Abortions. ANDREW A. MARCHETTI, M.D., F.A.C.S., Washington.

Discussion: DAVID N. DANFORTH, M.D., F.A.C.S., Evanston, Illinois.

Injuries of Cervix Producing Abortion. LEROY A. CALKINS, M.D., Kansas City, Kansas.

The Endometrium in Abortion. EDWARD C. HUGHES, M.D., F.A.C.S., Syracuse.

Discussion: ARTHUR T. HERTIG, M.D., Boston.

Endocrine Therapy in Abortion. EMMETT D. COLVIN, M.D., Atlanta.

Discussion: RONALD R. GREENE, M.D., Chicago.

Therapy of Incomplete Abortion. JOSEPH A. HARDY, JR., M.D., St. Louis.

Discussion: JAMES E. FITZGERALD, M.D., Chicago.

Thursday, October 8

What Constitutes Conservative Pelvic Surgery?

Moderator: FRANK R. LOCK, M.D., F.A.C.S., Winston-Salem.

For Menopausal Bleeding. JOHN I. BREWER, M.D., F.A.C.S., Chicago.

Discussion: ROBERT A. KIMBROUGH, JR., M.D., F.A.C.S., Philadelphia.

Cervical Lacerations, Erosions and Polyps. CLYDE L. RANDALL, M.D., Buffalo.

Discussion: HAROLD L. GAINEY, M.D., F.A.C.S., Kansas City, Missouri.

For Myomas. NORMAN F. MILLER, M.D., F.A.C.S., Ann Arbor.

Discussion: F. H. FALLS, M.D., F.A.C.S., Chicago.

For Infertility Due to Tubal Occlusion. To be announced.

Discussion: JOHN ROCK, M.D., F.A.C.S., Brookline.

Ovarian Tumors. GEORGE H. GARDNER, M.D., F.A.C.S., Chicago.

Discussion: HOWARD C. TAYLOR, JR., M.D., F.A.C.S., New York.

Friday, October 9

Surgical Complications of Pregnancy.

Moderator: SAMUEL A. COSGROVE, M.D., F.A.C.S., Jersey City.

Acute Abdomen. To be announced.

Ruptured Uterus. CHARLES J. SMITH, M.D., F.A.C.S. Chicago.

Lacerations of Cervix, Vagina and Vulva. JANET E. TOWNE, M.D., F.A.C.S., Chicago.

Carcinoma of the Breast. PETER A. NELSON, M.D., F.A.C.S., Chicago.

Benign Breast Lesions. ROBERT L. SCHMITZ, M.D., F.A.C.S., Chicago.

Indications for Cesarean Hysterectomy. M. EDWARD DAVIS, M.D., F.A.C.S., Chicago.

TRAUMA TO THE ABDOMEN

JAMES K. STACK, M.D., F.A.C.S., Chairman.

Tuesday, October 6

Moderator: FRANCIS D. MOORE, M.D., F.A.C.S., Boston.

The Systemic Effects of Trauma. FRANCIS D. MOORE.

Structural Vulnerabilities and Their Relationship to Abdominal Trauma. BARRY ANSON, M.D., Chicago.

Abdominal Wounds in Korea. JOHN M. OLNEY, M.D., Boston.

Burns and Wounds of the Abdominal Casing. HARVEY S. ALLEN, M.D., F.A.C.S., Chicago.

Posttraumatic Renal Insufficiency. To be announced.

Wednesday, October 7

Moderator: FRANK GLENN, M.D., F.A.C.S., New York.

Criteria for Treatment Priority in Multiple Injuries. FRANK GLENN.

Wounds of the Diaphragm, Stomach and Duodenum. CHAMP LYONS, M.D., F.A.C.S., Birmingham.

Wounds of the Small Bowel and Its Mesentery. J. DEWEY BISGARD, M.D., F.A.C.S., Omaha.

Injuries of the Large Bowel, Rectum and Perineum. R. ARNOLD GRISWOLD, M.D., F.A.C.S., Louisville.

Fractures of the Lumbar Spine and Pelvic Ring As They Relate to the Picture of Abdominal Trauma. THOMAS B. QUIGLEY, M.D., F.A.C.S., Boston.

Thursday, October 8

Moderator: CHARLES B. PUESTOW, M.D., F.A.C.S., Chicago.

Wounds of the Spleen and Its Vessels. To be announced.

Wounds of the Liver, Its Ducts and Its Vessels. To be announced.

Trauma and Its Impact on Pre-existing Abdominal Lesions. To be announced.

The Coroner's Physician's View of Fatal Abdominal Trauma. JERRY KEARNS, M.D., Chicago.

Friday, October 9

Moderator: CHARLES G. JOHNSTON, M.D., F.A.C.S., Detroit.

Injuries to the Major Vessels of the Abdomen and Pelvis. CHARLES G. JOHNSTON.

Diagnosis and Treatment of Rupture of the Kidney. J. HARTWELL HARRISON, M.D., F.A.C.S., Boston.

Injuries to the Bladder and Urethra. CARLISLE F. SCHROEDER, M.D., F.A.C.S., Detroit.

Injuries to the Female Genital Tract. RALPH A. REIS, M.D., F.A.C.S., Chicago.

Antibiotics in Abdominal Trauma. CHAMP LYONS, M.D., F.A.C.S., Birmingham.

SURGERY OF THE UPPER GASTROINTESTINAL TRACT

JOHN T. REYNOLDS, M.D., F.A.C.S., Chairman.

Tuesday, October 6

Esophagus

Benign Lesions:

Bleeding Esophageal Varicosities. ORMAND C. JULIAN, M.D., F.A.C.S., Chicago.

Tracheo-esophageal Fistulas. N. LOGAN LEVEN, M.D., F.A.C.S., St. Paul.

Esophageal Diverticulum, Pharyngeal and Epiphrenic. GUSTAF E. LINDSKOG, M.D., F.A.C.S., New Haven.

Hiatus Hernia. ANTHONY R. CURRERI, M.D., F.A.C.S., Madison.

Acute Burns of the Esophagus. Benign Strictures of the Esophagus. PAUL H. HOLINGER, M.D., F.A.C.S., Chicago.

Carcinoma of the Esophagus:

Carcinoma of the Upper Third of the Esophagus. DANELY P. SLAUGHTER, M.D., F.A.C.S., Chicago.

Causes of Mortality Following Resection of the Middle and Upper Third of the Esophagus. EDWARD F. PARKER, M.D., F.A.C.S., Charleston.

Palliative Operations for Carcinoma of the Esophagus. MARK M. RAVITCH, M.D., F.A.C.S., Baltimore.

Betatron Therapy for Carcinoma of the Esophagus. ROGER A. HARVEY, M.D., Chicago.

Wednesday, October 7

The Stomach and Duodenum

The Physiology of Gastric Secretion: Its Role in Peptic Ulceration. LESTER R. DRAGSTEDT, M.D., F.A.C.S., Chicago.

Symposium on Duodenal Ulcer.

Moderator. REGINALD H. SMITHWICK, M.D., F.A.C.S., Boston.

The Rationale of Surgical Approaches to Peptic Ulceration. To be announced.

Operations

Vagectomy for Peptic Ulceration. KEITH S. GRIMSON, M.D., F.A.C.S., Durham.

Gastrectomy for Duodenal Ulcer. HENRY N. HARKINS, M.D., F.A.C.S., Seattle.

The Management of Acute Duodenal Ulcers Near the Region of the Common Duct. HAROLD A. ZINTEL, M.D., F.A.C.S., Philadelphia.

The Problem of Massive Hemorrhage from Peptic Ulcer. ROBERT M. ZOLLINGER, M.D., F.A.C.S., Columbus.

Duodenal Diverticulum. MAX M. ZINNINGER, M.D., F.A.C.S., Cincinnati.

Thursday, October 8

Gastric Problems

The Problem of the High Lesser Curvature Ulcer and of One in the Lower Esophagus. RICHARD H. SWEET, M.D., F.A.C.S., Boston.

Gastric Ulcer: Difficulty of Differentiating from Carcinoma

Roentgenologist. E. L. JENKINSON, M.D., Chicago.

Internist. To be announced.

Surgeon. H. GLENN BELL, M.D., F.A.C.S., San Francisco.

The Role of Total Gastrectomy for Carcinoma of the Stomach. WILLIAM P. LONGMIRE, JR., M.D., F.A.C.S., Los Angeles.

Pouch Substitutes for the Stomach Following Total Gastrectomy. ARTHUR J. HUNNICUTT, M.D., F.A.C.S., Oakland.

The Cause and Prevention of Unsatisfactory Results Following Gastrectomy. To be announced.

Dumping Syndrome: Marginal Ulcer: Malnutrition.

Surgeon. JOHN H. MULHOLLAND, M.D., F.A.C.S., New York.

Internist. RALPH E. DOLKART, M.D., Chicago.

Friday, October 9

The Biliary Tract and Pancreas

Anatomy and Anomalies of the Biliary System and Pancreas. BARRY ANSON, M.D., Chicago.

Importance and Significance of Hepatic Function Tests in Jaundiced Patients. RICHARD B. CAPPS, M.D., Chicago.

Indications and Contraindications to Operations on the Biliary Tract. NATHAN A. WOMACK, M.D., F.A.C.S., Chapel Hill.

Surgical Errors in Biliary Tract Surgery. FRANK H. LAHEY, M.D., F.A.C.S., Boston.

Persistent Symptoms Following Cholecystectomy. HOWARD K. GRAY, M.D., F.A.C.S., Rochester, Minnesota.

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